rates, yielding an age-standardized cancer death rate that depends to some extent on each of the 18 separate rates.

There are important reasons for examining separately trends in age-standardized mortality at ages above and below 65, because the population estimates are less reliable at older ages, and for many types of cancer errors of death certification at ages over 65 may be so numerous, especially earlier this century, as to distort the apparent trends in the all-ages age-standardized death certification rates quite seriously.

Obviously, age-standardized rates calculated by different authors can be compared directly with each other only if the weights that the different authors have chosen to use are the same, and since most other recent commentators on U.S. cancer onset or death rates seem to have used weights that are proportional to the age distribution of respondents to the U.S. 1970 census (table A1), we have done likewise when we wanted an all-ages standardized death rate. Moreover, when we wanted to calculate age-standardized rates among people aged 65 and over, we have used the last five weights in table A1 for the 5 age groups 65–69, 70–74, 75–79, 80–84, and over 85 (and, of course, zero weights for the first 13 age groups). Likewise, of course, to calculate age-standardized rates among people under age 65, we have used only the first 13 weights in table A1.

In table A2 we give a detailed example of the calculation of our three age-standardized lung cancer death certification rates for U.S. males in 1977. Obviously, the age-standardized rate of 0.31796/thousand males under age 65 could equally well be expressed as 317.96/million or 31,796/100 million. Since there are currently about 100 million American males (and about 100 million females) under age 65, if annual rates for people under 65 are expressed per 100 million, they are numerically of a similar order of magnitude to the annual numbers of cancer. We have therefore presented all our age-standardized cancer rates under age 65 as rates per 100 million, so that they suggest to the reader the approximate annual numbers of cancer deaths involved. Likewise, since there are currently only about 10 million American men (and about 10 million women) aged 65 or over, we have presented all rates among such people as rates per 10 million. Thus we would describe the respective age-standardized rates among men under 65 and among men over 65 that were calculated in table A2 not as 0.31796 and 4.0497/thousand (which misleadingly suggests far fewer cancers among the young), but rather as 31,796/100 million and 40,497/10 million, which correctly suggest the approximate numbers of deaths involved.[4] Readers who would prefer the more usual rates (per thousand or per million) can easily recover them, of course, merely by adjusting the decimal point.

One cannot make valid inferences about increases or decreases in the underlying causes of cancer from examination of trends in the percentage of all deaths attributed to cancer (since this is affected by changes in mortality rates from other diseases), nor from examination of trends in the total number of cancers per year or in the crude cancer rates (because both are affected by purely demographic changes). These propositions are generally accepted by all competent epidemiologists (though not by all propagandists), and we would like to see it equally widely accepted that it is also dangerous to make inferences from trends in overall age-standardized cancer rates if these trends are due chiefly to trends among older people and are not also evident upon examination of the trends in the age-standardized rates among people under age 65. This is not because the deaths of old people are less important, nor because trends among them may be determined by social changes which took place half a century or more ago, but simply because the data on cancer trends among old people are often less reliable. This assertion is documented in subsequent appendices.

Time to Tumor

We have deliberately chosen not to express any of our serious analyses in terms of "latency," "reduced latency," "mean age at onset of tumor," or similar indices, because such concepts and the statistical meth-

TABLE A1.—*Weights used for calculating age-standardized cancer onset rates or death rates (as "weighted averages" of age-specific rates)*

These weights are based on the age distribution of a typical million respondents to the U.S. 1970 census, and so the age-standardized cancer rates that are calculated using these weights are described as "rates standardized to U.S. 1970," or some equivalent phrase.

Age range		Weighting factor	Sub-total of weighting factors	Grand total of weighting factors
No.	Years			
1	0–4	84,416	901,258 (<65 years of age)	1,000,000 (all ages)
2	5–9	98,204		
3	10–14	102,304		
4	15–19	93,845		
5	20–24	80,561		
6	25–29	66,320		
7	30–34	56,249		
8	35–39	54,656		
9	40–44	58,958		
10	45–49	59,622		
11	50–54	54,643		
12	55–59	49,077		
13	60–64	42,403		
14	65–69	34,406	98,742 ≥65 years of age)	
15	70–74	26,789		
16	75–79	18,871		
17	80–84	11,241		
18	≥85	7,435		

[4] Moreover, if these different units are used below age 65 and above age 65, then the all-ages age-standardized rate per 100 million happens to be roughly equal to the sum of the two separate rates, which is a convenient approximation to bear in mind. (Strictly, the all-ages rate per 100 million is 0.901258 times the standardized rate per 100 million at ages 0–64 plus 0.98742 times the standardized rate per 10 million at ages >65.)

APPENDIX A: AGE STANDARDIZATION PROCEDURES

The age-standardized cancer death certification rates we have utilized are chiefly rates per *100 million* standardized directly to the age distribution of the U.S. 1970 census respondents aged *under 65*, rates per *10 million* standardized to the age distribution of respondents aged *65 or over*, or rates standardized to the age distribution of all 1970 census respondents. The age standardization procedure is described in detail, with an example, as are our reasons for using these unusual denominators, i.e., 100 or 10 million. We have everywhere used age-standardized rates rather than either crude rates or such potentially misleading concepts as "mean latency" or "mean age at diagnosis."

Crude Rates, Age-Specific Rates, and Age-Standardized Rates

Throughout this century in the United States, the total probability of death before age 65 years has been decreasing fairly steadily, and it is now less than half what it was only 50 years ago. Consequently, the percentage of the U.S. population that is over 65 years old has been increasing fairly steadily, and the percentage that is over 75 years old is more than double what is was half a century ago. Throughout the world, old people have probably always been several dozen times more likely to develop cancer in the near future than are young people, and so the increase (due chiefly to the decreases in other causes of death) in the percentage of old people tends to increase the annual percentage of the whole population that will get cancer (i.e., the so-called crude total cancer onset rate). This phenomenon is not in itself any cause for alarm—rather the reverse, in fact—but it does mean that we must allow for the steady increase in the proportion of old survivors at high risk of cancer if we wish to use trends in the onset rate of cancer to determine whether the external causes of cancer are more active now than long ago. When we turn our attention from the aggregate of all cancer and examine the many different types of cancer separately, exactly the same applies, of course. The *crude* death rate from each particular type of cancer (total cases in one year divided by total population) not only depends on the onset rate of such cancers among people of a given age, but also depends very strongly on the proportions of the population who are young, middle aged, and old.

Two generally accepted methods of calculating indices of cancer mortality (or, instead, cancer incidence[1]) that are not in expectation materially affected by the age distribution of the population as a whole are to calculate either age-specific or age-standardized rates, and we have chiefly adopted the latter.

The *age-specific* death rate from some particular type of cancer (e.g., stomach cancer) among some particular population (e.g., U.S. males) is the death rate among the males in some particular narrow range of ages. By convention, the 18 five-year age ranges 0–4, 5–9, 10–14, etc. up to 75–79, 80–84, and finally 85 and over, are usually adopted for the calculation of age-specific death rates.[2] For any one particular type of cancer, separate examination of the variation with time of many of the separate age-specific rates may yield much more understanding than any less detailed analysis would have done. (*See* the discussion of trends in U.S. lung cancer mortality in appendix E for an example of this.) However, we wish to characterize, at least approximately, the current trends in each of several different types of cancer, and tabulation of all the trends in the age-specific rates for each of them would produce such an overwhelming mass of numbers that they would be difficult to grasp, and we have chosen to fall back on the use of age-standardized rates instead.

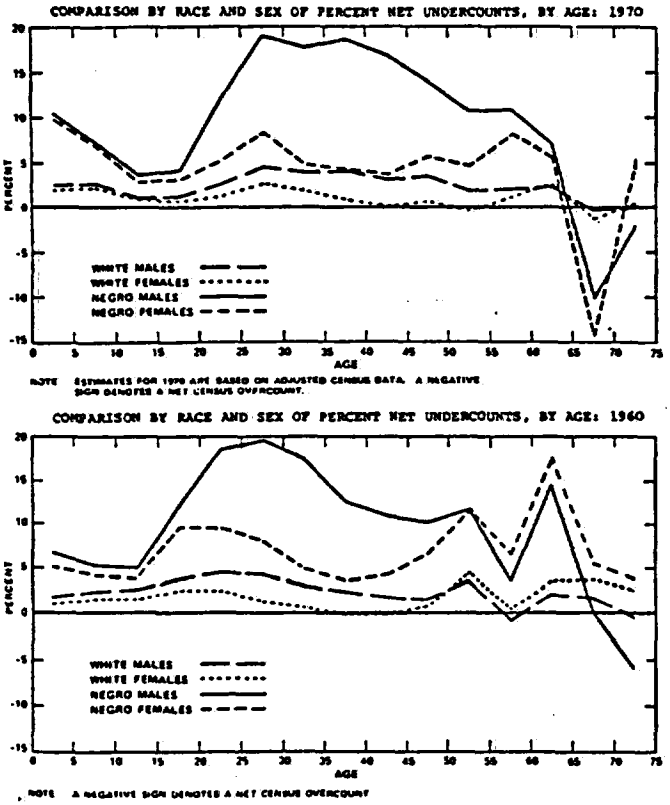
The *age-standardized* cancer rates that we, together with most other commentators on U.S. national data, have used are then simply defined as a weighted average[3] of the 18 separate age-specific rates. Obviously, the age-standardized rate that we actually calculate by such a procedure depends strongly on which weights we choose to adopt. For example, if we gave positive weights to the first 13 age-specific male stomach cancer death rates (i.e., those for ages 0–4, 5–9, etc. up to 60–64), and zero weights to the last five such rates (65–69, etc.), then we would effectively be ignoring all cancers in people aged 65 or over, and the result might be referred to as "an age-standardized stomach cancer death rate among men *aged under 65*." Conversely, we might do the opposite, giving zero weights to the first 13 age-specific stomach cancer death rates and calculating the age-standardized stomach cancer death rate among men *aged 65 and over*. As a final alternative, we could have done what most other commentators have done and give positive weights to all 18 age-specific

[1] Cancer *mortality*, or cancer *death*, rates count only those cancers that cause death (or that directly cause some other disease, such as pneumonia, perhaps, which then causes death), whereas cancer *incidence*, or cancer *onset*, rates count all cases, fatal or not.

[2] Some authors have subdivided the human life-span into decades, or into even longer periods of time, when they calculate age-specific death rates. However, if within some of these large age ranges both the numbers of people at risk and the disease onset rate vary rapidly with age, then the use of such long subdivisions of the human life-span may lead to slight uncertainties of interpretation, especially for those types of cancer such as lung cancer or prostate cancer whose onset rates vary most rapidly with age. By contrast, calculations of the effects of even quite sharp dependencies of both population and disease on age suggest that such difficulties will have no material effects (except, perhaps, in the age range ≥85) if the life-span is subdivided into the 18 standard *five*-year age groups.

[3] A weighted average of 18 rates is obtained by first choosing 18 multiplying factors, or "weights"; multiplying each observed cancer rate by its corresponding weight; adding up all these 18 products; and, finally, dividing this total by the total of the 18 weights to obtain the weighted average or age-standardized cancer rate. This procedure is also called "direct age standardization."

States who would leave America if they were dying, but it includes those of them who would not and who would get into the National Center for Health Statistics publications if they died. Clearly, the decennial census is a crude tool for estimation of appropriate denominators, especially since a few percent of whites and 10 or 20% of non-whites are unregistered in any given census. Also, many people (especially non-whites) seem to have their age described incorrectly by the person who completes the census return for the household they live in, so that the U.S. Bureau of the Census' own estimates of the percentage undercount vary markedly with age and color in a manner that is not even constant from census to census (text-fig. B1). "Adjustment" of the crude census figures for the "estimated" degree of undercount is necessary, but the available estimates of census undercount are so large, especially for non-whites, and depend so erratically on age that it is difficult to trust either the unadjusted or the adjusted data for non-whites (especially since various different methods of estimation of the degree of undercount considered by the Bureau of the Census, 1974, yielded discrepant results). Also, the "adjusted" estimates for the 1950's that have been published by the Bureau of the Census are strikingly inconsistent with the unpublished adjusted estimates for the 1960's which the Bureau of the Census provided for us (unless there really was a sudden 50% increase in the number of



TEXT-FIGURE B1.—Comparison of the estimated percentage undercount in the two most recent published U.S. censuses by age and race, showing marked differences (Bureau of the Census, 1974).

males aged 85 and over between 1959 and 1960[1]).

Moreover, there is no reason to suppose that the dividing line between white and non-white on death certificates used by physicians or state officials when they complete the forms corresponds exactly with the self-completed dividing line between white and non-white on census returns. If there are systematic discrepancies, these will cause systematic errors in the death rates for whites and, particularly, for non-whites If there are time trends in these discrepancies, they will cause artifactual trends in death rates (especially for non-whites) which can be avoided only by pooling both "white" and "non-white" numbers of deaths and population estimates, the ratio of which yields the all-races death rates that we have chiefly used.

We thus require population estimates in each calendar year from 1933 to 1978 (subdivided by sex and age) which include members of the armed forces stationed overseas, which are corrected as accurately as possible for estimated census undercount, and which cover the same states as the annual publication of numbers of deaths (i.e., including Alaska from 1959 and Hawaii from 1960). Such estimates have been constructed (but not published) by the Bureau of the Census for 1960–78 and, by non-comparable methodology, for 1950–59, but not for earlier years. This is unsatisfactory because it means that the absolute numbers of deaths that were tabulated at considerable U.S. government expense each year from 1933 to 1959 cannot be converted easily into death rates that can be compared with modern rates. We therefore relied on the following ad hoc estimates for 1933–59.

1933–39.—We had available to us only estimates that excluded the (then few) members of the armed forces stationed overseas.

1933–49.—We had available to us only estimates that were not corrected for census undercount, which will result in death rates that are a few percent high before 1950.

1959.—Of the available estimates for 1959 that are corrected for census undercount, none include Alaska. Since Alaska contributes only 0.3% of all U.S. deaths, the error can be adequately rectified for 1959 by the use of the corrected population estimates for the contiguous United States in 1959 plus the uncorrected estimate for Alaska in 1960.

1950–59.—Population estimates, corrected for census undercount, have been made available to us by L. Miller, Bureau of the Census, but are increasingly clearly erroneous at ages 75–79, 80–84, and ≥85. On the advice of J. G. Robinson, Bureau of the Census, we took estimates of census undercount on April 1, 1950 and April 1, 1960 among white males age >75,[1]

[1] For white males, Robinson estimated 5.31% overcount in 1950 and 0.1% overcount in 1960. For white females, the corresponding figures were 0.90% undercount in 1950 and 4.1% undercount in 1960. For non-white males, they were 13.21% overcount in 1950 and 13.9% overcount in 1960. For non-white females, they were 22.89% undercount in 1950 (!) and 1.0% overcount in 1960.

TABLE A2.—Example: *Calculation of age-standardized lung[a] cancer death certification rates among males in 1977*

Age range		No. of 1977 male deaths certified as being due to lung[a] cancer at indicated ages[b]	Estimated[c] male population in indicated age range in mid-1977 (thousands)	Annual age-specific male lung[a] cancer death certification rates/1000	Weight (based on U.S. 1970 census; *see* table A1)	Product: age-specific rate × weight	Annual age-standardized death certification rate/1000
No.	Years						
1	0–4	2	8,090	0.0002	84416	21	—
2	5–9	5	9,051	0.0006	98204	54	—
3	10–14	2	9,922	0.0002	102304	21	—
4	15–19	10	10,896	0.0009	93845	86	—
5	20–24	24	10,404	0.0023	80561	186	—
6	25–29	55	9,378	0.0059	66320	389	—
7	30–34	147	8,016	0.0183	56249	1032	—
8	35–39	423	6,397	0.0661	54656	3614	—
9	40–44	1,119	5,740	0.1949	58958	11494	—
10	45–49	2,921	5,879	0.4969	59622	29623	—
11	50–54	5,780	5,863	0.9858	54643	53869	—
12	55–59	8,607	5,425	1.5865	49077	77863	—
13	60–64	11,495	4,500	2.5544	42403	108316	—
14	65–69	12,987	3,704	3.5062	34406	120635	—
15	70–74	11,479	2,592	4.4286	26789	118638	—
16	75–79	7,972	1,648	4.8374	18871	91286	—
17	80–84	4,241	1,018	4.1660	11241	46830	—
18	≥85	2,038	674	3.0237	7435	22481	—
1–13	0–64	30,590	99,561	—	901258	286568	0.31796[d]
14–18	>65	38,717	9,636	—	98742	899871	4.0497[d]
1–18	All ages	69,307[e]	109,197[e]	—	1000000	686439	0.6864[d]

[a] In this example, we have included not only lung but also all other respiratory tract cancers except larynx.

[b] Excludes 5 men certified as dying of such cancers (*see* footnote *a*) but with their age at death not known, and probably also excludes well over 5,000 who actually died of lung cancer but were certified as having died of some other type of cancer, of "cancer, site not known," or even of some cause other than cancer. Conversely, various other fatal diseases (especially other cancers that spread to the lungs) may be miscertified as lung cancer. The likelihood of both types of error is greater among men aged ≥65 yr than among younger men.

[c] The population estimates that we used differ from those used by most other authors, in that we have included members of the armed forces serving overseas (because we thought that those developing fatal cancer were likely to return home and be numbered among American deaths) and, more importantly, in that we have used population estimates which have been corrected for census undercount (Bureau of the Census, personal communication; *see* appendix B). In most decennial censuses, a few percent of American whites and *ten to twenty* percent of American non-whites either do not appear at all on census returns or appear with misreported age. If such people were to die of lung cancer their deaths would be included in the numerators of the age-specific rates, so they should also appear in the denominators. Corrected population estimates, however, were available to us only from 1950, so from 1933–49 we have, perforce, used the standard (uncorrected) population estimates.

[d] Total of products divided by total of weights.

[e] The *crude* death rate is 69,307/109,197, or 0.63/1,000.

ods that they engender often yield conclusions that are seriously misleading and rarely (if ever) yield important insights which are not available from examination of the age-specific and age-standardized rates. The reasons for this are discussed in some detail in Appendix 3 to the statistical annex to IARC (1980). *Note* particularly that although arguments based on the supposed effects of carcinogens on tumor latency may suggest that the determinants of particular types of cancer in middle and old age may be very different, we see no good reason to believe this (once temporary cohort effects have been ironed out by the passage of time, in the manner described for lung cancer in appendix E).

APPENDIX B: POPULATION ESTIMATION FOR CALCULATION OF AGE-SPECIFIC RATES

Even in the United States as a whole, the available population estimates (whether or not corrected for census undercount) seem surprisingly unreliable, especially at age 65 and over or especially for non-whites. In the particular areas covered by cancer registries, the uncertainties in estimates of the population at risk may perhaps be even larger. The population estimates we have used for 1950–78 include, wherever possible, both members of the armed forces stationed overseas and people who did not complete their previous decennial census. (Published corrections for "census undercount" require some ad hoc modification for 1950–59.)

Ideally, one would like to use as a denominator for the calculation of age-specific rates all the people who if they had developed cancer would have been counted in the numerator of our rates. For mortality, this ideal denominator includes all people abroad (such as Americans on vacation or business, or members of the armed forces abroad) who would return home and die in the United States if they were to develop cancer. It excludes visitors or legal or illegal immigrants in the United

Errors of incidence registration.—Although incidence data discriminate more reliably between the different types of cancer and are not affected by trends in the curability of particular types, they are affected by the large trends over the last 30 years in the readiness of medical services to register all new cases and (especially recently) by the registration of more and more lumps that are histologically cancer but biologically benign.

Errors of estimation of cure rates.—Estimates of case-fatality rates are subject to many of the same biases that affect estimation of incidence rates, so attempts to correct trends in mortality for trends in curability may in some cases yield less accurate estimates of the trends in real onset rates than the uncorrected trends in mortality might have done.

The origins and effects of these three sources of error are discussed separately below.

Errors of Death Certification

First, cancer patients may die of their cancer without this fact being recognized and may even be certified as having died of some totally different cause, such as pneumonia (for primary or metastatic lung cancer), stroke, senility (for primary or metastatic brain cancer), kidney failure (for myeloma), or some infective disease (for various leukemias or lymphomas). Conversely, patients who did not really die *of* cancer may be miscertified as having done so. In a special enquiry by the British Registrar General into the true causes of some 14,000 deaths in British hospitals in 1959, one-fifth of the deaths thought by the clinician to have been due to cancer were probably due to other causes, whereas a similar number of deaths that the clinicians had not attributed to cancer were probably due to cancer (Heasman and Lipworth, 1966). Many of these clinical errors would not have appeared on death certificates, but many of them would have, and deaths not in hospital might be even less reliably certified than deaths in hospital.

A missed diagnosis of cancer in a dying patient is presumably more likely to occur among old cancer patients than among young ones, if only because the old ones are less likely to be hospitalized. Such errors are likely to have been progressively reduced over the past few decades, particularly in old people since the introduction of Medicare in 1965. We note, for example, that the operation rate in the 10 years after 1965 rose by 45% in men and women age 65 years or over compared with increases of 11 and 17%, respectively, at ages 15-44 years and 45-54 years (National Center for Health Statistics: Unpublished data, and Weiss R: Personal communication). If, as seems likely, fewer diagnoses of fatal cancer are missed nowadays, these changes in medical practice are likely to have caused an artifactual increase in total cancer death certification rates, especially among older people, and the relationship of cancer death certification rates to age should have been less steep half a century ago than it is today.

Text-figures C1 and C2 show that this is indeed the case, although the effect seems marked only among octogenarians, among whom, if one judges by the shape of the age-incidence graphs in these text-figures, about half of the cancer deaths during the 1930's may have been missed. Alternatively, the population estimates for octogenarians may have been particularly in error, but whatever the reasons artifactual trends in cancer death certification rates are probably more extreme in old age than in middle age. We have therefore examined separately the trends in mortality at ages under 65 (standardized to the age distribution of the U.S. 1970 census respondents under age 65: *See* appendix A) and at older ages (standardized to the older 1970 census respondents).

Second, patients known to be dying with widespread cancer may never have the site of primary origin of their cancer determined, and 6-8% of American cancer death certificates are for "cancer of an unspecified primary site." This percentage is a little lower among whites than among non-whites, and among middle-aged than among older people, but it has not materially changed for decades. Therefore, it may not seriously bias the assessment of trends in cancers of specified sites. However, the 20-odd thousand cancer deaths of an unspecified site each year do represent an uncomfortably large amount of missing information, especially since we do not know, of course, which particular sites have their true death rates most distorted by these exclusions.

Third, patients dying of cancer of one primary site (e.g., lung) may be misdiagnosed as having a cancer originating from another site (e.g., pancreas or brain) if the cancer has either extended itself to other nearby organs or metastasized to distant organs. For example, Boyd et al. (1969), in a special investigation of bone tumor death certificates, concluded that at ages over 65 most so-called "bone tumors" were in fact misdiagnosed secondaries from other sites, and the same may well have been true in the past for liver cancer because bone and liver are not sites where cancers commonly arise, but, along with brain and lung, they are sites to which cancers commonly spread. For Britain in 1959, Heasman and Lipworth (1966) concluded that about one-fifth of the clinical diagnoses of cancer in hospitalized patients specified the wrong site for the primary, and there is no reason to believe that American hospitals were much better (although again it must be noted that not all of these clinical errors would have resulted in incorrect death certificates). Likewise, cancers of one particular cell type may be misdiagnosed as cancers of another cell type; for example, pleural mesotheliomas may be misdiagnosed as ordinary lung cancer or vice versa and myeloid and lymphoid leukemia may be confused with each other, especially in previous decades; all of the different non-Hodgkin's lymphomas may be confused with each other; and malignant and benign fatal brain tumors may be

TABLE B1.—*Population estimates (person-years) used in principal analyses of rates and trends*
Thousands of person-years, corrected for census undercount, including armed forces overseas.

Years*	Estimated person-years (thousands) for ages:																	
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	≥85
White male																		
A	41991	38118	31047	25547	24888	27485	28443	27081	25347	23235	20230	17987	15904	12483	8709	5240	2558	1138
B	45062	42226	38328	31260	25887	25291	27392	28257	26583	24698	22322	18788	16054	13523	9960	6213	3098	1481
C	43390	45397	42502	38619	31596	26235	25396	27166	27821	25815	23644	20819	16758	13556	10691	7070	3722	1860
D	38133	43714	45719	42742	38703	31764	26404	25385	26970	27154	24877	22104	18723	14192	10572	7519	4207	2287
E	34474	38290	43906	45837	42725	38760	31837	26337	25183	26337	26218	23317	20001	15986	11205	7449	4558	2817
F	6620	7312	7993	9148	9026	8204	7224	5885	5026	5067	5182	4933	4105	3388	2436	1541	914	632
White female																		
A	39989	36315	29660	24559	23965	26608	27925	26725	25186	23343	20579	18823	17118	13935	10445	6855	3749	1880
B	42984	40250	36540	29945	25120	24541	26852	28190	26671	24981	23026	19889	17807	15762	12250	8306	4625	2600
C	41388	43347	40553	36910	30590	25735	24837	26985	28195	26396	24556	22383	18871	16412	13914	9892	5775	3367
D	36317	41729	43692	40904	37359	31099	26062	25043	27048	27944	26007	23842	21417	17437	14497	11335	7072	4511
E	32745	36508	41949	43917	41142	37644	31292	26139	25062	26767	27510	25197	22819	19891	15549	11929	8312	6107
F	6279	6961	7635	8762	8694	7965	7061	5829	5019	5101	5411	5329	4655	4202	3386	2504	1733	1459
Non-white male																		
A	6826	5578	4494	3865	3636	3649	3832	3626	3270	2735	2410	1931	1432	991	619	354	180	102
B	7906	6877	5666	4557	3911	3725	3717	3725	3325	2991	2562	2124	1673	1199	771	445	221	128
C	8166	7939	6946	5715	4580	3938	3810	3781	3522	3052	2760	2326	1808	1368	922	541	288	156
D	7669	8161	7993	6970	5698	4594	3969	3818	3695	3380	2892	2469	2053	1452	1028	645	342	217
E	7653	7778	8304	8108	7039	5795	4707	4032	3797	3567	3232	2619	2191	1699	1098	706	422	294
F	1536	1584	1607	1697	1575	1336	1062	895	772	741	664	589	431	375	242	148	86	73
Non-white female																		
A	6759	5515	4444	5841	3603	3610	3656	3328	3098	2653	2392	2013	1599	1180	816	503	322	269
B	7804	6812	5607	4509	3914	3739	3780	3669	3262	3001	2608	2211	1836	1420	974	606	328	271
C	8047	7848	6885	5666	4588	4008	3854	3852	3608	3172	2897	2488	1980	1607	1197	749	415	272
D	7550	8047	7900	6938	5782	4730	4117	3928	3824	3533	3077	2700	2312	1687	1348	964	565	425
E	7482	7674	8175	8042	7168	6085	4951	4238	3966	3763	3475	2910	2537	2059	1407	1069	756	658
F	1499	1557	1583	1677	1593	1406	1130	944	818	783	721	656	510	463	319	217	159	173

* A=years 1953–57, B=1958–62, C=1963–67, D=1968–72, E=1973–77, F=mid-1978 only. The estimated person-years for each 5-year period is the sum of the mid-year populations for the 5 separate years that it spans, and so equals five times the average population in those years.

interpolated linearly between them for July 1, 1950, July 1, 1951, etc. to July 1, 1959, and adjusted the uncorrected 1950–59 census-derived population estimates for white males age 75–79, 80–84 and ≥85 by these interpolated factors. This was repeated separately for white females, for non-white males, and for non-white females.

The population estimates described above are listed in table B1 for 1953–78. Scrutiny of them revealed none of the large-scale resurrection of the dead that is suggested by the uncorrected census-based population estimates that many other analyses of U.S. cancer death rates have utilized.

APPENDIX C: SOURCES OF BIAS IN ESTIMATING TRENDS IN CANCER MORTALITY, INCIDENCE, AND CURABILITY

When assessing either past or current age-standardized rates of cancer incidence or mortality, and particularly when assessing the trends in those rates as we move from the past to the present, certain sources of error must be recognized. For a few cancers, the rates of increase (e.g., lung cancer or melanoma) or decrease (e.g., stomach cancer or cervical cancer) are so large and have continued for so long that it is easy to be sure of their direction and approximate magnitude. However, for most other types of cancer the trends of increase or decrease in their age-specific onset rates over the past decade or two seem much less marked, and it is therefore difficult to estimate these trends reliably. If trends are assessed incautiously, biases in the data may be more important determinants of the apparent trend than the real underlying trends in onset rates will be, which is clearly unsatisfactory. Apart from possible errors in population estimation, which have been discussed in appendix B, there are three main categories of error.

Errors of death certification.—For various reasons, the number of American deaths certified as being due to a particular type of cancer may be substantially in error, especially at age 65 and over or in the years before 1950. For certain types of cancer, however, the best available estimate of the trend in onset rates may be the trend in mortality rates since 1950 among people under age 65.

site of origin of the cancer, as diagnosed in hospital, and the primary site of origin of cancer, as it eventually appeared on the death certificate, for 82,000 patients in the TNCS. Many discrepancies emerged. Half the cases of rectal cancer were eventually miscertified (chiefly as colon cancer, of course), as were about 20% of all cases of cancer of the lymphoid tissues, buccal cavity, thyroid gland, liver, gallbladder, larynx, cervix and other uterus (the latter two not only as each other), and about 10% of the cases of most other types of cancer. The effects of misdiagnosis and/or miscertification can be circumvented to some extent by adding together into groups the rates for cancers (e.g., all intestinal tumors, all non-Hodgkin's lymphomas, all benign or malignant brain tumors, all leukemias, all lung tumors) that are particularly often confused with each other and also by restricting attention to patients under age 65.

Fifth, treatment may improve sufficiently to have a noticeable effect on total national mortality rates, as has happened over the past decade or two for Hodgkin's disease and for various tumors of uncommon embryomal tissues. (The recent decrease in Hodgkin's disease death rates is, of course, largely or wholly real, and we consider it as a source of "bias" only because we wish to use trends in death rates to indicate trends in onset rates.) The End Results Program (1976, 1980) has estimated the 5-year relative survival rates for various categories of patient, but their method (surveillance of all registered new cancers in one area and of all patients admitted with cancer to certain hospitals in other areas) may be subject to appreciable distortion due to artifactual trends in hospital referral or in the completeness of incidence registration of the nonfatal cases (*see* below). There are thus no wholly reliable data on cancer cure rates. However, it seems safe to conclude that there have been no large increases in the cure rates for the common cancers, so for these the trends in death certification rates may approximate reasonably well to the real trends in real disease onset rates. We shall return to the question of trends in cure rates when we have discussed the artifacts that may affect trends in incidence rates.

Errors of Incidence Registration

Many of the biases listed above that affect cancer death certification rates also affect registered incidence rates, but six additional biases are peculiar to incidence data.

First, population estimation may be more difficult. Our uncertain estimates of the ages and numbers of people in the whole United States were reviewed in appendix B. The uncertainties must presumably be even worse for registry data, where the aim is to count deaths and cases in a defined area (e.g., Detroit, Mich.) with no legal constraints on migration. When is a resident not a resident? The difficulties in estimating the population at risk of getting a cancer that would get registered seem almost as formidable as the problem of registering the cancers. We do not know how well the population estimates for the SNCS and TNCS really corresponded with the population from whom the registered cases were drawn or whether some of the unexplained discrepancies that we shall discuss between the incidence rates calculated in the 1969-71 TNCS and in the 1973-77 SEER Program derive in part from errors of population estimation.

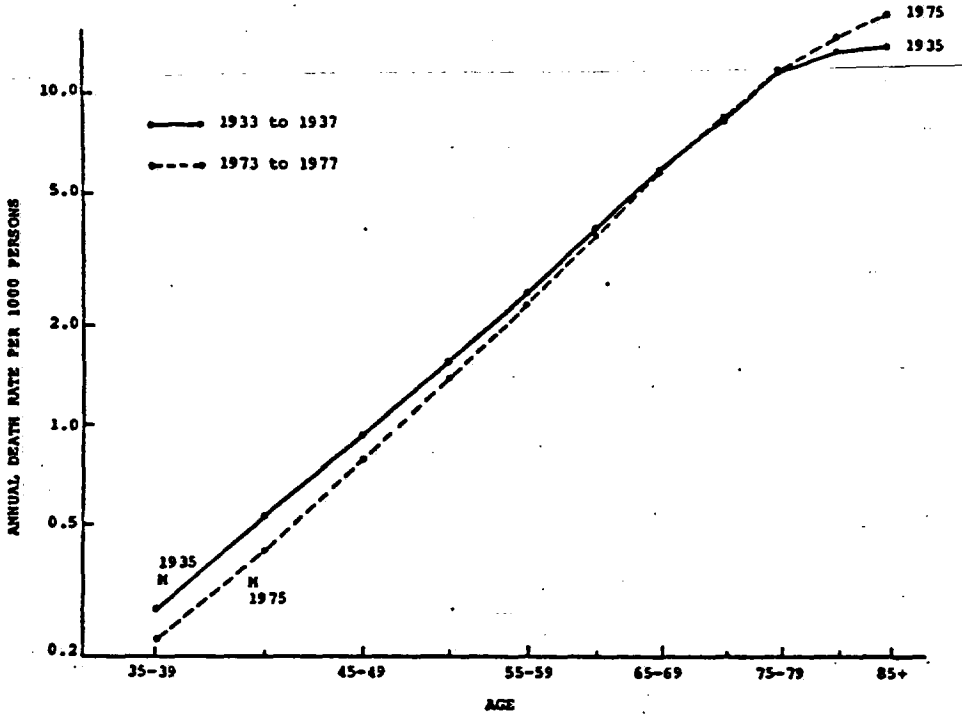
Second, people only die once and do so at a reasonably well recorded time. By contrast, the symptoms of a cancer may develop gradually, and the patient may attend several medical institutions for diagnostic investigations and treatment, with the age and the spelling of the name varying from one place to another. When all these visits are monitored, it is difficult to arrange a system of record linkage which ensures that this patient gets counted exactly once. Perhaps the problems of mistakenly including the same case twice, or of mistakenly including cases that were first diagnosed before the beginning of the official study period, were worse in earlier years, inflating the cancer onset rates recorded in the 1947/8 SNCS.

Third, standards of diagnosis may improve. A decreasing percentage of cancers (7.3% in the SNCS and only 4.6% in the TNCS) were of liver, bones, or an unspecified site. (This is, of course, a bias that will affect mortality data as well as incidence data.)

Fourth, biases in *registration* rates may be caused by a progressive improvement in the readiness of physicians in the area to collaborate with a cancer registry. For example, Connecticut has maintained one of the best cancer registries in the United States for 45 years, yet table C1 suggests that throughout this period the completeness of their coverage of non-fatal cancers may have been improving so rapidly as to introduce very substantial upward biases into any estimates of trends or of survival rates[1] in those very cancers for which (because an appreciable proportion are curable) registration rates might differ significantly from death certification rates. Likewise, in the Second and Third National Cancer Surveys (in 1947/48 and in 1969-71) the respective proportions of cases that were ascertained by death certificate only, and for which no clinical record was ever found, were 11.2 and 2.2%, suggesting that the earlier survey may have underestimated total incidence rates by about 10%. (*See* footnotes to table C1.)

Fifth, the definition of what constitutes a cancer may change. For example, all salivary gland tumors, whether malignant or of mixed cellularity, were counted up to 1967, but the mixed tumors were dropped thereafter (because their histologic nature was uncertain, but their biologic behavior was usually benign). Likewise, all brain tumors were included in the SNCS, whereas only those specified as malignant were included in the TNCS. This procedure caused a substantial artifactual

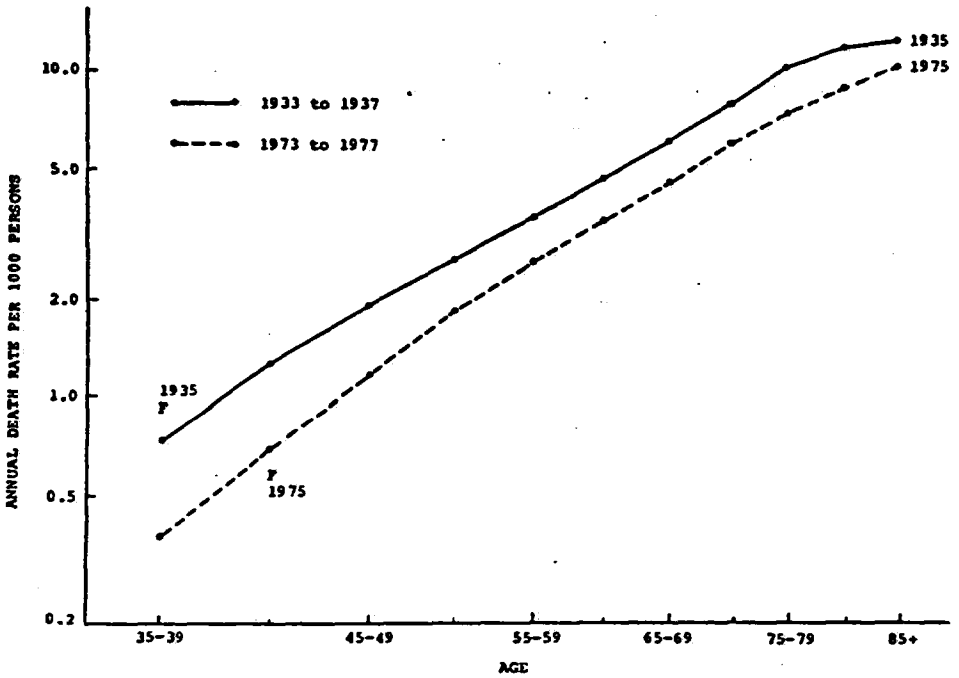
[1] The cases listed by the Connecticut Cancer Registry comprise nearly half of the material on which the End Results Program (1976, 1980) have estimated trends in cancer cure rates.



TEXT-FIGURE C1.—Non-respiratory cancer death rates in U.S. males by age, 1935 and 1975 (all races).

confused. There have certainly been substantial changes in the differential diagnosis of the various leukemias and lymphomas, and there may also have been appreciable trends in the differential diagnosis of the various solid tumors, to judge by the fact that in the Second and Third National Cancer Surveys (in 1947/48 and 1969–71) the respective percentages of cancers that were not microscopically confirmed were 26.5 and 9.9%.

Fourth, even if a cancer is correctly diagnosed while the patient is still alive, the correct information may never reach the death certificate. Percy et al. (1981) have tabulated the correspondence between the primary



TEXT-FIGURE C2.—Non-respiratory cancer death rates in U.S. females by age, 1935 and 1975 (all races).

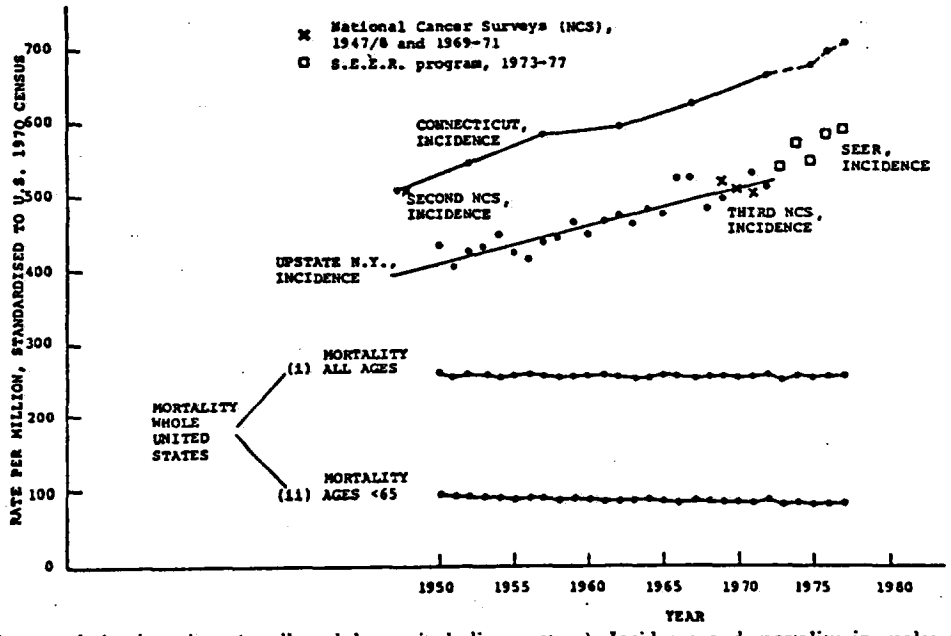
tumor by a non-fatal type of tumor, by biases in death certification at ages under 65, or by any systematic differences between Connecticut and the United States as a whole. If so, it can be accounted for plausibly only by *a*) improvements in therapy or *b*) biases in incidence registration rates. It seems most unlikely that treatments for the common tumors have improved sufficiently to account for more than a small fraction of the divergences apparent in text-figure C3. (Certainly, the large irregularities in the female incidence data must be artifactual.) The most plausible explanation, therefore, seems that errors in these registered incidence data produce errors in the apparent trends that are much larger than the real underlying trends.

Before accepting this conclusion, however, we shall examine in more detail the trends in mortality and in registered incidence for three particular types of cancer (intestines, breast, and prostate). These three types have been chosen for two reasons: *a*) They are sufficiently common as causes of death to be of substantial public health importance, and *b*) the proportion of diagnosed cases that do not cause death is large enough for differences between incidence and mortality rates to be of substantial interest. (Three other types of cancer—lung, stomach, and pancreas—are also among the six most important causes of death listed in table 1 on page 1197, but for each of these the large majority of diagnosed cases are so rapidly fatal that the differences between incidence and mortality are of less interest.)

Cancer of the intestines.—To render comparable the data on the incidence and mortality of intestinal cancer, we have pooled all intestinal sites, including rectum. (On death certificates, cancers are often described as "intestines, site unspecified," or "large intestine, site unspecified," or "colon, subsite unspecified," a practice that is much less common in the incidence data collected by a good cancer registry. Moreover, there is an increasing tendency not to specify the intestinal subsite on death certificates, and there is substantial nosologic confusion between colon and rectum: *See* appendix D.)

Cancer of the intestines is not difficult to diagnose, even without modern aids, and the surgical treatment of intestinal cancer has not undergone major changes since 1950. To our regret, however, such large discrepancies between the trends in the incidence and in the mortality data were still evident (text-fig. C4) as to suggest the paradoxical conclusion that the rates of change of death certification yield more reliable information about trends in incidence during the 1960's and 1970's than can trends in registered incidence in New York or Connecticut. (Similar discrepancies between trends in registered incidence and trends in certified mortality are, of course, evident among the data for cancer of the female intestines, for which during the past quarter of a century the certified mortality has been decreasing while the registered incidence has been rising. Such discrepancies are also present for cancers of many other sites.)

We have also plotted (text-fig. C4) the data on intestinal cancer incidence provided by the Second National Cancer Survey in 1947/48 (SNCS), by the Third National Cancer Survey in 1969–71 (TNCS), and by the ongoing Surveillance, Epidemiology and End



TEXT-FIGURE C4.—Cancer of the intestines (small and large, including rectum): Incidence and mortality in males in the U.S., 1947–77. *Pre-publication access to 1973–77 SEER data (including 1973–77 Connecticut data) to appear in Young et al., 1981, was by courtesy of the Biometry Branch, NCI (E. S. Pollack, Director). Pre-publication access to 1935–74 Connecticut data (April 1978 tape) to appear in Heston et al., 1981, was by courtesy of the Connecticut Cancer Epidemiology Unit (J. W. Meigs, Director). Our other sources of incidence data are New York State Department of Health, 1976, Dorn and Cutler, 1955, and Cutler and Young, 1975.*

TABLE C1.—*Percentages of patients whose cancers were ascertained by death certificate only and for whom no medical details subsequently could be found:[a] Connecticut Cancer Registry, 1935–74[b]*

Years	Cancer							
	Lung		Breast	Prostate	Colon		Pancreas	
	Male	Female	Female	Male	Male	Female	Male	Female
1935–39	32	38	24	39	33	35	46	54
1940–44	28	36	15	23	24	32	30	45
1945–49	24	19	10	15	17	19	32	29
1950–54	17	21	7	12	13	14	24	25
1955–59	15	13	6	9	11	11	21	24
1960–64	8	6	3	5	4	6	9	9
1965–69	2	3	1	2	1	2	4	5
1970–74	2	2	1	1	1	1	2	5

[a] The percentages that would not have been registered but for the death certificate are higher than the percentages cited in this table. (This is because in some instances finding the death certificate may have directed attention to a medical record that would otherwise have been overlooked.) The cited percentages, moreover, are percentages of *all* tumors, fatal or non-fatal, that were ascertained by death certificate only, and so are not as high as the percentage of *fatal* tumors that would not have been registered but for the death certificate. The percentages of non-fatal tumors that were not registered is, of course, not known directly but may also have been large in the earlier years.

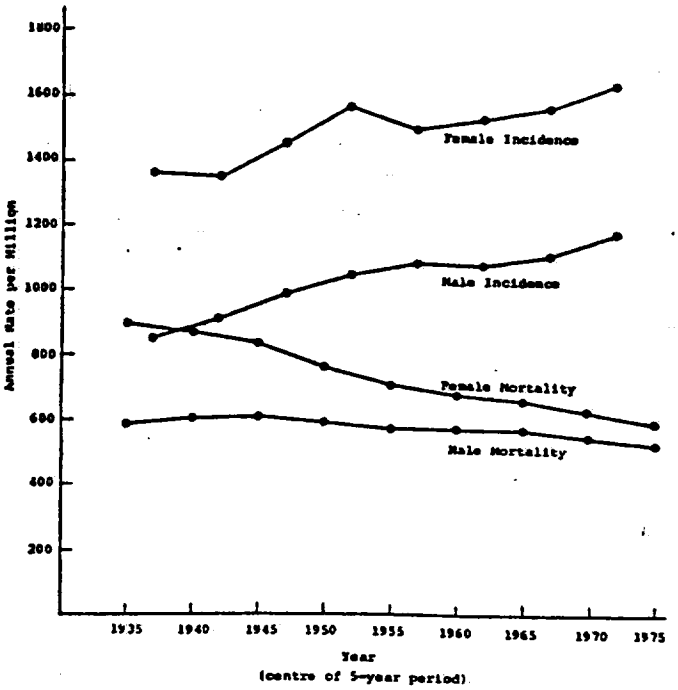
[b] Data in tables C1 and C4, and in text-figures C3 to C6, are by courtesy of the Connecticut Cancer Epidemiology Unit (*see* legend to text-fig. C4).

decrease in brain tumor incidence between the two surveys (Devesa and Silverman, 1978). (The distinction between benign brain tumors, brain tumors of unspecified histology, and malignant brain tumors is particularly difficult on death certification data as well because all types may cause death.) Another important change in the opposite direction seems to be an increasing tendency for what would have been called "bladder papillomas" to be termed "carcinomas."

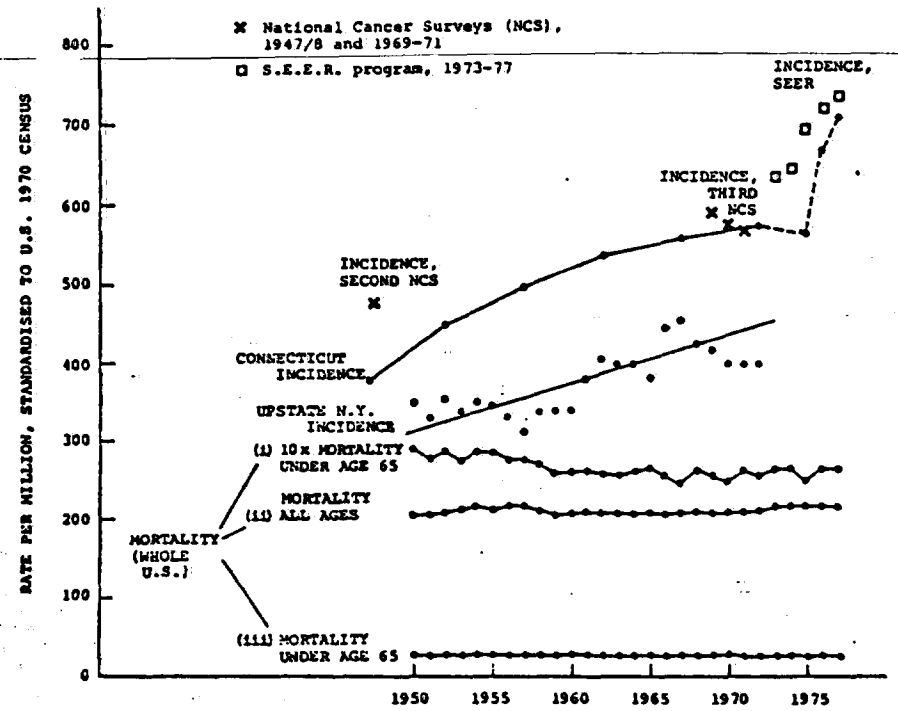
Sixth, one of the most serious sources of error in comparing cancer registration rates in different years stems from the increasingly vigorous search for lumps, because by old age the human body may contain various lumps that, if examined histologically, would be classified as cancer, yet that are biologically so benign that they will not cause any serious symptoms in what life-span remains. For example, by age 70 2.5% of males in the areas covered by the TNCS can expect to have been diagnosed as having had prostate cancer (and the annual incidence rate of new cases is only 0.4%, some of which remain quiescent even if treated conservatively), whereas 25% of the prostate glands of 70-year-old males who die of unrelated causes would, if examined by standard methods, be found to contain "cancer" (Breslow et al., 1977). Likewise, among women undergoing mastectomy for cancer of one breast, and in whom cancer is not already clinically evident in the opposite breast, for many subsequent years 0.5% per year can expect cancer to become clinically evident in the opposite breast; whereas if the opposite breast is sampled and examined histologically at the time of the original operation, 15–20% will already contain "cancer" (Fox, 1979). The scope for biased trends in "incidence" which are due to either more complete registration of what cancers are found or to the finding of "cancers" that would never have caused serious disease is disturbingly large. (A high prevalence of such "incidental" neoplasms is also found in many strains of experimental animals; and even after standardized laboratory autopsy and tissue preparation procedures, animal pathologists often have difficulty agreeing which to call malignant, benign, or merely hyperplastic.)

Comparison of Incidence and Mortality

Trends in total cancer mortality are dominated by the rapid increases in lung cancer, for which (at least since 1950) the differences between incidence and mortality are not important because the case fatality has remained very high. Cancer incidence is dominated by skin cancer, which is in almost all cases so easily cured that many registries do not even attempt to register it. Excluding lung and skin, and excluding people over age 65, we have plotted total U.S. cancer mortality rates 1933–77 against calendar year and compared these with the corresponding total incidence rates in Connecticut (text-fig. C3). The divergence between the two trends is substantial for each sex, and is unlikely to be accounted for by replacement of some fatal type of



TEXT-FIGURE C3.—Age-standardized certified death rates for entire U.S. population, 1933–77, contrasted with Connecticut registered incidence rates, 1935–74; all cancers except lung and skin. *Rates per million, standardized to the age distribution of all respondents under 65 yr to the U.S. 1970 census, as described in appendix A.*



TEXT-FIGURE C6.—Cancer of the prostate in males in the U.S.: Incidence and mortality, 1947-77. *For data sources, see text-fig. C4.*

The erratic pattern of variation of the eight data points from TNCS and the SEER Program in text-figure C5 (1969-77) is not explicable by any other obvious source of errors. Although many of the 10 TNCS geographic areas differed from the 10 SEER areas, 4 geographic areas were common to the two studies, and the erratic pattern of the 1969-77 data is virtually unchanged if attention is restricted to these 4 common areas (Pollack and Horm, 1980). Finally, the standard errors on each of these eight points are negligible (≈1.1%) compared with the 25% rise in "incidence" recorded between 1971 and 1974.

The same sudden large increases in "incidence," unmatched by any concomitant increases in mortality, were seen in Finland as nationwide breast cancer screening was introduced (Gāstrin, 1980). For breast even more than for intestinal cancer, trends in mortality seem much more reliable than trends in incidence, *unless* the trends in incidence are assessed by comparison of the SNCS and TNCS. Comparison of SNCS and TNCS suggests (either by good luck or good management) trends in incidence that are reasonably compatible with the trends in mortality.

Prostate cancer.—Here again, the scope for bias is large, especially since prostate cancer affects the old more than the young to a greater extent than any other cancer. Therefore, prostate cancer incidence (and mortality) trends are especially dependent on the age groups in which both the number of cancers and the estimates of the population at risk are least reliable. A possible great source of difficulty may be that if the prostate glands of men aged 70 who have died of completely unrelated causes, with no clinical history of prostate cancer, are examined post mortem, *1 in 4* (25%) will be found to have "prostate carcinoma" (Breslow et al., 1977). By contrast, by the age of 70 only about 3% of men, even at the SEER incidence rates, will have been diagnosed as having developed clinically evident prostate cancer. (If someone ever invents a method of screening apparently healthy men for prostate cancer, the apparent incidence rates may be expected to rise quickly by several hundred percent!)

Text-figure C6 contrasts the trends in the available incidence data with those in the national mortality data for prostate cancer. It differs from text-figures C4 and C5 in that the mortality data for under age 65 are presented twice, both as they actually are and also multiplied by a factor of 10 merely to make the pattern discernible, because cancer of the prostate gland is an uncommon cause of death before age 65. It also differs from the earlier figures in that, because one-half of all cases of prostate cancer affect men over 75, the uncertainties in the population estimates for the older male age groups in the 1950's cause appreciable irregularities in the all-ages age-standardized rates.

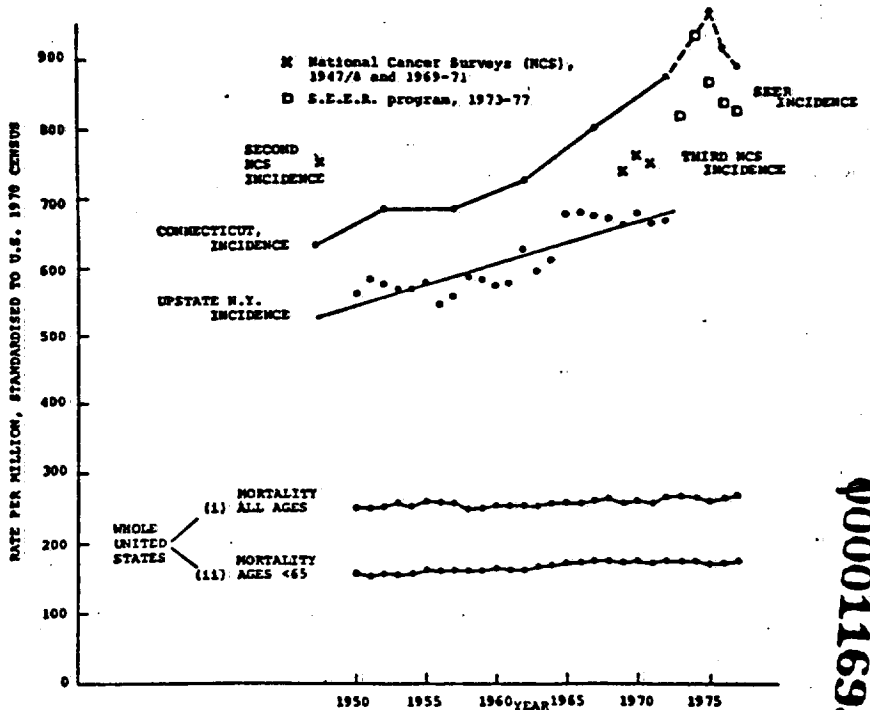
As before, however, the mortality data at ages under 65 suggest no material increase in prostate cancer onset rates; whereas the incidence data collected in Connecticut and New York suggest marked upward trends, and the trend suggested by comparison of the TNCS and SEER data with each other is absurdly incompatible with the mortality data. For prostate cancer, the comparison of the SNCS and TNCS data also suggests some increase in incidence, though an increase that is much more moderate. A moderate increase such as this is compatible with a fairly constant true disease onset

Results (SEER) Program in 1973-77, each of which covered about 10% of the U.S. population. Comparison of SNCS with TNCS suggests the same sort of constant incidence as is suggested by the mortality data, and if attention is restricted to ages below 65, a gentle decrease in both mortality (0.4%/yr) and incidence (0.8%/yr) is suggested. By contrast, comparison of the TNCS data with the SEER data suggests a very rapid increase that is even steeper than the one suggested by the longer-term Connecticut and New York data and that is completely incompatible with the gentle and steady long-term decreases in mortality. We are, therefore, unwilling to trust these particular short-term changes in apparent incidence as useful evidence about trends in real cancer onset rates in the 1970's. They may be due in part to more frequent screening for the presence of an intestinal tumor by examination of the feces for small amounts of blood, to the development of colonoscopy as a method of examining the colon, and to the classification of borderline polyps as "malignant" tumors.

Breast cancer.—The trends in age-standardized female breast cancer mortality are almost constant, though very slightly upward. It is likely that these trends are a reasonably accurate reflection of the underlying onset rates of serious breast cancer because the primary treatment of breast cancer (by surgery and/or radiotherapy) did not alter much between the 1950's and the 1970's, while the chemotherapy of early breast cancer was not in common use, and fatal breast cancer is, again, not a difficult disease to diagnose. (During 1968-78 the apparent trends in age-standardized breast cancer mortality have been 0.1% per annum downward among women under age 65 and 0.7% per annum upward among older women, yielding an average of 0.2% per annum upward for all women. *See* appendix D for discussion of possible causes of these small trends in terms of age at first pregnancy, following Blot, 1980.)

By contrast, with the sole exception of the SNCS-TNCS comparison, the available data on breast cancer incidence exhibit bizarre fluctuations from year to year, which are far too large to be ascribable to chance (text-fig. C5). In upstate New York, where a cancer registry has been in operation since 1940, there has been an average increase of about 1% per annum over the past quarter century, a substantial increase which is hardly reflected at all in the mortality data. When the data from the TNCS are compared with those from the SEER Program, wild fluctuations are evident in registered incidence rates during the 1970's that are likewise not reflected at all in the mortality data. These fluctuations can have little or no biological reality and must, in part at least, be determined by fluctuations in public and professional interest, causing many lumps that would not otherwise have been diagnosed as breast cancer to be removed, classified as "locally invasive," and counted among the incidence data. Fox (1979) has already argued that there are numerous breast lumps that are "histologically cancer but biologically benign." To support this argument, Fox noted that although 15-20% of women with cancer in one breast would be found to have "cancer" in the opposite breast if the opposite breast were immediately biopsied, the rate of clinical appearance of cancer in the opposite breast if no biopsy is taken is only 0.5% per year over many subsequent years.

TEXT-FIGURE C5.—Cancer of the breast in females in the U.S.: Incidence and mortality, 1947-77.
For data sources, see text-fig. C4.



no deaths have actually been delayed. (This last bias may particularly affect breast cancer, but it should not have much effect on most other common cancers which are either completely cured or rapidly fatal.)

Second, patterns of referral to the hospitals collaborating with the End Results Program might alter significantly over a period of a quarter of a century, although it is difficult to predict what the effects of this might be. That this may be so is suggested by the 1-year relative survival rate of 86% for patients with "localized" prostate cancer in 1950–54; surely, 14% of such patients cannot have been killed within a year merely by a localized cancer of the prostate gland, so was their localized prostate cancer diagnosed because of investigation for some life-threatening disease? By 1970–73, the 1-year relative survival for localized prostate cancer had increased to 93%, though the standard therapy (excision and irradiation) had not changed. It is difficult to explain this and to explain the peculiarly large change in 5-year relative survival rates for cancer of the prostate gland as a whole, except in terms of trends in biasing factors.

Because of these various uncertainties, it is a matter of judgment which of the improvements in reported cure rates in table C2 are to be accepted as largely real. The increases over the past quarter century of 5–10% in the 5-year relative survival rates for most of the common cancers (table C2) are very much an extreme upper limit on the amount of improvement which it is plausible to accept, rather than a direct estimate of the actual amount of improvement. The corresponding lower limit on the amount of improvement that it is plausible to accept is zero, and the truth lies somewhere in between. Our view is that the sevenfold improvement in reported leukemia cure rates among people under age 35 must be largely or wholly real (and will probably continue in the late 1970's), as must the twofold improvements in Hodgkin's disease (from one-third relative survival in the 1960's to two-thirds in the early 1970's). However, for many of the common cancers the improvements do not seem to us to be materially larger than bias alone would suggest, and as we do not have evidence for any large improvements in *curative* treatment,[2] we suspect that there has been substantially less change in case fatality rates than even the 5 or 10% improvements in reported case fatality rates would suggest. Therefore, for most types of cancer the changes in mortality over the past quarter century should certainly be within a few percent, or even less, of the fractional changes in real onset rates.

Conclusion: Which Indicators of Real Trends in Cancer Onset Rates are Most Reliable?

We have compared trends in mortality with trends in incidence for the few major sites and have found that for those particular sites there are discrepancies too large to be explained plausibly without postulating the existence of serious upward biases in the trends in age-standardization cancer registration rates in both Connecticut and New York since 1950. Similar conclusions would have emerged had we chosen to study certain other sites, and this remains true whether rates of change of incidence and mortality both derive from the same geographic area (table C3) or not (table C4).

By contrast, the trends in onset rates suggested by

TABLE C3.—*Difference between percentage annual rates of change of registered incidence[a] in upstate New York[b] and of certified mortality[a] in upstate New York[b]*

When the difference between these two percentages is positive, which it almost always is, it indicates that registered incidence has been increasing relatively faster than the certified mortality, due perhaps to improvements in therapy during 1960–72 (e.g., for Hodgkin's disease), perhaps to more rapid rectification of biases in registration than of death certification (e.g., for intestines), or perhaps to decreases in overcertification (e.g., liver).

Type of cancer	Annual percentage rate of change of incidence (1950–72) minus annual percentage rate of change of mortality (1960–72)	
	Male	Female
Mouth, pharynx, larynx, or esophagus	0.5	1.7
Lung	1.2	−1.2
Stomach	−0.2	0.0
Intestines	0.9	1.0
Liver	3.2	2.3
Gallbladder	0.5	0.7
Pancreas	1.3	1.2
Melanoma	1.3	0.3
Breast	—	0.6
Bladder	2.4	2.5
Kidney	1.9	1.8
Cervix uteri	—	0.9
Endometrium	—	1.4
Ovary	—	0.9
Prostate	1.6	—
Testis	1.5	—
Brain (malignant only)	1.9	1.5
Leukemia	1.5	1.4
Hodgkin's disease	3.1	1.9

[a] Standardized to U.S. 1970 census, as in appendix A.
[b] Data in this table are from the publication by the Bureau of Cancer Control (1976) of the New York State Department of Health.

[2] Even if cancer patients are subdivided into "stages" (e.g., Stage I = no regional or distant spread of the disease, Stage II = regional but not distant, Stage IV = distant spread), no direct assessment of whether therapy has improved can be based on trends in 5-yr survival of patients of a given stage. This is because the steady improvements in the care or technology with which regional or distant disease is sought will, perhaps surprisingly, produce artifactual improvements in prognosis in *each* stage. In Stages I and II this improvement is due to removal of those having micrometastases, whereas in Stage IV it is due to dilution of those having gross metastases by those having micrometastases. Despite these tendencies, the percentage of prostate cancers recorded as "localized" has been increasing over the past quarter century, presumably indicating an increase in the detection as Stage I tumors of lesions that are of borderline significance biologically.

rate, slightly biased by progressively more detection as "carcinomas" of biologically benign prostatic neoplasms.

A repeat publication of the SNCS–TNCS comparisons already reported by Devesa and Silverman (1978) but with the data standardized to *a*) U.S. 1970 0–64, *b*) 1970 65+, and *c*) all U.S. 1970 would be useful for many purposes, as would similarly standardized publication of other registry data. (Alternatively, the truncated rates for ages 35–64 recommended in IARC, 1976 would do, and might be better for international purposes.) The age-specific, site-specific data have been published for the total of all areas surveyed in the SNCS and TNCS, and, although they do not allow a comparison to be restricted to the seven areas common to both surveys (or separate examination of melanoma and non-melanoma skin), we have examined the apparent trends among people below 65 years of age in appendix D, table D5, on page 1286.

Errors in Estimation of Cure Rates

We are not chiefly concerned in this report with trends in the treatment of cancer, but rather with trends in the causes of cancer and hence in cancer onset rates. However, since we intend to use trends in cancer mortality as an indication of trends in cancer onset rates, we shall review some of the evidence on trends in cure rates. The most widely accepted data are those reported by the End Results Program (1976, 1980), reviewing the survival of all 169,000 cancer patients registered in Connecticut during 1950–73 and of 284,000 cancer patients seen at a few dozen particular hospitals (mostly in California) over the same period. Despite these large aggregate numbers, some particular types of cancer are so rare that only a few dozen or a few hundred cases are available for study in each period of a few years (e.g., 1950–54 or 1970–73). Omitting all of these rare types except Hodgkin's disease and leukemia, for both of which decreases in the case-fatality rate are so large that random errors are relatively unimportant, we list in table C2 the 5-year relative survival rates observed in certain time periods. There is a general tendency for these survival rates to be slightly better in the 1970's than in the 1950's (e.g., the 5-year relative survival rate recorded for cancer of the female breast has risen from 60% in 1950–54 to 68% in 1970–73). Before this increase can be accepted as evidence for an important improvement in therapy, however, one must ask: What substantial biases might affect the recorded relative survival rates?

First and foremost, many of the biases that we have previously discussed in relation to incidence data might bias the recorded survival rates. In the 1950's, many cases were discovered only via the death certificate, with some earlier medical record then being traced as a result of inquiries initiated because of the death. Such methods clearly underestimate the normal duration of survival in earlier periods. Likewise, in the more recent periods there may have been more breast or prostate lumps or bladder papillomas discovered that were considered histologically cancer though being biologically benign, accentuating any upward biases in the trends in curability. Finally, if incurable breast lesions are diagnosed earlier nowadays than in the 1950's, then the 5-year survival may seem better, even if

TABLE C2.—*Estimated 5-year relative[a] survival percentages among whites: United States, 1950–73*

Type of cancer[b,c]	Patients' sex	Relative survival percentages for patients diagnosed in years: 1950–54	1955–59	1960–64	1965–69	1970–73
Stomach	♂	12	12	10	12	12
	♀	11	13	14	14	14
Colon	♂	40	41	42	46	47
	♀	42	47	45	47	50
Rectum	♂	38	39	36	41	43
	♀	43	40	41	45	48
Pancreas	♂	1	1	1	1	2
	♀	2	2	2	2	2
Larynx	♂	52	56	55	63	63
	♀[d]					
Lung	♂	5	7	8	8	9
	♀	9	9	11	13	14
Breast	♀	60	62	64	65	68
	♂[e]					
Cervix uteri	♀	59	60	59	57	64
Endometrium	♀	72	71	73	75	81
Ovary	♀	30	29	34	34	36
Prostate	♂	43	49	52	57	63
Bladder	♂	54	55	58	62	61[f]
	♀	51	56	58	62	60[f]
Kidney	♂	33	36	38	41	44
	♀	34	39	39	43	50
Brain	♂	19	21	20	25	[g]
	♀	22	25	29	33	[g]
Hodgkin's disease	♂	28	36	36	53	66
	♀	34	39	48	57	69
Leukemia[h]	—	—	—	—	—	—

[a] A *relative* 5-yr survival of 100% would indicate a risk of death no worse than that of the U.S. population as a whole in the relevant time period (matched, of course, for age and sex).

[b] These are the sites for which the End Results Program (1976, 1980) reported on the survival of about 1,000 or more cases/time period, together with Hodgkin's disease and leukemia.

[c] The data refer to all patients diagnosed as having malignant disease of the type specified, irrespective of pathologic stage.

[d] Inadequate data on cancer of the ♀ larynx.

[e] Inadequate data on cancer of the ♂ breast.

[f] Any progressive tendency to class bladder papillomas as bladder carcinomas will produce a progressive but artifactual increase in the relative 5-yr survival rates for bladder "cancer." (*See also* footnote *g*.)

[g] Changes in the histologic definition of "brain tumor," excluding certain categories of non-malignant tumor, make the reported 5-yr relative survival rates in 1970–73 (♂, 18%; ♀, 22%) difficult to compare with the rates for earlier periods.

[h] Because of recent advances in the treatment of childhood leukemia, it is preferable to examine trends in survival separately for leukemia patients aged <35 yr (~25% of all leukemia patients).

Year of diagnosis	Leukemia <35 yr: 3-yr relative survival percentage	Leukemia ≥35 yr: 3-yr relative survival percentage
1950–59	5	22
1960–66	10	22
1967–73	24	20

as well not waste time with anything but the mortality data. However, it may be advisable at least to examine both incidence and mortality data, even though the mortality data seem generally more trustworthy. Our tabulations of both, therefore, appear in appendix D.

APPENDIX D: U.S. AGE-STANDARDIZED CANCER DEATH RATES DURING THE PAST FEW DECADES

This appendix presents the detailed data on which the rather general assertions in section 4.1 about trends in cancer mortality during the past few decades were based.

Trends in Total Cancer Mortality Since 1933

After the long list in appendix C of possible biases and difficulties of interpretation, the actual mortality data seem (either refreshingly or deceptively!) simple and straightforward. Table D1 gives trends in age-standardized death certification rates since 1933 (the first year for which all states had to notify the causes of all deaths centrally) for people under 65, and table D2 gives the same trends for older people. The cancer death rates are subdivided into "respiratory" cancer[1] and "non-respiratory" cancer, since the respiratory cancers are dominated by lung cancer and are available as a reasonably consistently defined category throughout 1933–77.

Overall, there are clearly no epidemic increases in mortality from the aggregate of all non-respiratory types of cancer—rather the reverse, in fact—and we discuss the trends in lung cancer mortality in more detail in appendix E. On the basis of appendix E, we conclude that among people under age 65 the increases (and decreases, among younger males) in respiratory cancer death certification rates are mostly real, at least since 1950, and can be largely or wholly[2] accounted for by the effects of cigarette smoking, as long as proper allowance is made for the many decades that elapse between the onset of regular cigarette smoking and its full effects on lung cancer. Contrary to common belief, age-specific total death rates are still improving, and were it not for the substantial ill effects of cigarette smoking (both on respiratory cancer and on the aggregate of all causes of death except neoplasms), Americans would be living in a time of even more rapidly decreasing age-specific death rates, both in middle age and in old age, than is already the case.

Trends in Site-Specific Cancer Mortality Since the Middle of the Century

It is uncertain how far back trends in American cancer death certification rates can be relied on (and the reliability is different for old and young and for different types of cancer, of course), but 1950 seems a sensible starting point for the estimation of modern trends, at least for the solid tumors. In 1950 there were new rules for coding death certificates, there was a new census (and population estimates corrected for estimated census undercount are available from the Bureau of the Census only from 1950 onward), the classification of cancer had just begun to be based on a reasonably modern International Classification of Diseases (the 6th ICD), so that, for example, Hodgkin's disease was classified as a neoplasm (rather than as an infective disease!), and the lymphomas were listed separately, and the important distinction between cancer of the cervix and other uterine cancers had recently begun. Moreover, by 1950 fairly modern standards of diagnostic radiology already existed, and non-toxic anesthesia and the chemotherapy of infective diseases had just developed, allowing large aseptic operations to help cure abdominal or thoracic cancers that had not already metastasized (and making it less likely that pneumonia or tuberculosis caused by unrecognized primary or secondary cancer in the lung would cause the death of a patient and therefore be miscertified as the underlying cause of death). Finally, although there have been some notable recent advances in the cure of certain leukemias, lymphomas, and tumors of embryomal tissues, there have been no corresponding advances in the cure of the common cancers since 1950 (*see* appendix C). Therefore, for many cancers the trends since 1950 in death certification rates among people under age 65 are probably a useful indicator of the real trends in disease onset rates in recent decades.

The data for the period since 1950 for the aggregate of all non-respiratory cancers are subdivided (in table D3 for people under 65 and in table D4 for older people) into as much detail as routine Government publications will allow. A more detailed breakdown, covering mortality during 1950–67, is given in the excellent National Cancer Institute Monograph No. 53 (Burbank, 1970); another more detailed breakdown, covering both mortality (1935–74) and incidence (1947–71, comparing the Second and Third National Cancer Surveys, SNCS and TNCS) is given by Devesa and Silverman (1978, 1980). Because Devesa and Silverman did not examine incidence rates separately among people over and under age 65, we have calculated these (table D5).

If attention is restricted to people aged under 65, then for almost all types of cancer except for those strongly affected by smoking (that is, the cancers of the respiratory and upper digestive tracts), the most recent

[1] Chiefly lung (and related tissues) but also including the larynx and nasal area but not the pharynx or mouth.

[2] Although the trends in mortality from lung and other respiratory tract cancers do not *of themselves* suggest the existence of any new causes of lung cancer other than cigarettes (and suggest if anything a diminution in the causes other than tobacco of cancer of the larynx and of the aggregate of the remaining respiratory sites apart from the lung), this fact may merely be due to lesser, yet important, effects of other factors being difficult to pick out reliably because of the large effects of cigarettes. For discussion, *see* appendix E.

TABLE C4.—*Incidence trends minus mortality trends*

Annual percentage increase of registered incidence in Connecticut (comparing 1950–54 with 1970–74) minus annual percentage increase in certified mortality in the United States as a whole (comparing 1953–57 with 1973–77). Two comparisons are made, one between trends in incidence and trends in all-ages mortality, the second between trends in incidence and trends in under-age-65 mortality.

Type of cancer, males	Trend in Connecticut minus trends in the rest of United States: Difference[a] between annual percentage rates[b] of change among males	
	Mortality, all ages, vs. incidence, all ages	Mortality, ages <65, vs. incidence, all ages
Mouth, pharynx, larynx, esophagus	−0.4	−1.3
Remaining respiratory (chiefly lung)	−0.1	0.9
Stomach	1.1	0.8
Intestines, including rectum	1.2	1.3
Liver, gallbladder, and bile ducts	0.8	0.8
Pancreas	0.4	0.7
Bladder	2.9	4.1
Kidney	1.1	1.8
Prostate	1.6	1.6
Brain and other parts of the nervous system	0.1	2.0
Leukemia	1.6	2.1
Hodgkin's disease	3.3	3.6
Non-Hodgkin's lymphomas	−0.5	1.3

[a] As in table C3, a positive difference indicates that the annual percentage increase in incidence exceeds that in mortality.
[b] All rates are standardized to the U.S. 1970 census population, as described in appendix A.

comparison of the Second and Third National Cancer Surveys (SNCS and TNCS) with each other do seem more consistent with the concurrent trends in mortality, and so although the registration rate, especially for tumors that are not uniformly fatal, may be subject to various moderate biases,[3] comparison of these two surveys seems a reasonable basis for estimation of the approximate trends in incidence for most solid tumors, except those of the brain and perhaps bladder and salivary gland. The comparison of these two surveys has been well presented by Devesa and Silverman (1978; *see* also Devesa and Silverman, 1980), in parallel with a discussion of the concurrent trends in mortality, and we shall not reproduce their detailed tabulations, though a graphic presentation of some of their SNCS-TNCS comparisons appears in text-figs. 5 and 6 on page 1211. Since comparison of the SNCS and TNCS might be slightly more reliable if attention were restricted to ages under 65, and also if "all races" were presented, this comparison is provided in table D5 on page 1286.

The one comparison of incidence rates that seems completely unreliable is that based on the Third National Cancer Survey, 1969–71 (TNCS) and the Surveillance, Epidemiology and End Results (SEER) Program, 1973–77. Quite fantastic and irregular variations in incidence are suggested by such comparisons (either between the two studies or within SEER), ten times greater than could plausibly be attributed to chance, and a hundred times greater than the corresponding annual changes in mortality over the past few decades. Perhaps because some other commentators have not examined the TNCS-SEER trends on the same graphs as the SNCS data and the long-term trends in mortality, our conclusion that the TNCS-SEER trends are unreliable is not widely accepted. Various commentators, among them the Toxic Substances Strategy Committee (TSSC, 1980), in their recent report to the President of the United States, have concluded, *chiefly on the basis of Pollack and Horm's (1980) comparison between TNCS and SEER*, that real cancer incidence rates are increasing rapidly (at 1.3%/yr in males and 2.0%/yr in females). We have given good reasons for distrusting this method for determining incidence trends for the common cancers and see no reason to trust it for the less common cancers. Pollack and Horm (1980) at least express a reasonable degree of caution in their conclusions, but the TSSC does not, and in its main text it generates a firm (and ill-founded, in our view) impression that epidemic increases in cancer are now in progress over and above those attributable to tobacco (appendix E). Anyone who, examining the data in text-figures C4, C5, and C6, can conclude that the most reliable estimate of trends in cancer onset rates is that provided by the TNCS-SEER comparisons deserves a medal for bravery. We have instead preferred to estimate current trends in U.S. cancer onset rates approximately by comparison of the Second and Third National Cancer Surveys, and, more reliably (at least for many of the common cancers), by examination of the trends since 1950 in the age-standardized death rates among people of all races under age 65.

Our argument that "the SNCS-TNCS comparison may be reasonably accurate because it is reasonably consistent with the mortality trends among people under age 65" is, of course, rather circular. After all, if we allow only incidence data that indicate trends exactly identical with the trends in mortality, we might

[3] Certain such biases might be expected to produce discrepancies between the SNCS–TNCS trends in incidence and the national trends in mortality for those cancers for which neither diagnostic procedures nor cure rates have undergone material change since 1947. Reassuringly, after standardization for age and sex, the 63% decrease in the stomach cancer death rate between 1947 and 1970 was exactly matched by a 64% decrease in the registered incidence rate of stomach cancer between the SNCS and the TNCS. Despite this reassurance, of course, net biases of about 0.5%/yr in either direction could easily exist, with some types of tumor affected differently from others. Unfortunately, the magnitude of this uncertainty is as great as the magnitude of changes which, if real, would be scientifically important.

TABLE D2.—*U.S. age-standardized rates[a] of death certification[b]/10 million people aged 65 years or over, 1933–77*

There are at present ~10 million ♂ and 10 million ♀ 65 years old or over in the United States, so the cited rates are roughly similar in magnitude to the actual annual numbers of such deaths.

Because this table relates wholly to people over 65 years old, all the cancer rates in it are likely to be somewhat unreliable, but the rates for the earlier years are even more unreliable than those for the more recent years.[b]

See table D1 for explanations of footnote letters.

Type of cancer	Rates[b]/10 million people, aged 65 yr or over, for:									
	Earlier years[b]				More recent years					
	1933–37 (~1935)	1938–42 (~1940)	1943–47 (~1945)	1948–52 (~1950)	1953–57 (~1955)	1958–62 (~1960)	1963–67 (~1965)	1968–72 (~1970)	1973–77 (~1975)	1978 only
Males										
All causes except neoplasms[c]	815,135	771,843	722,222	682,546	655,477	661,568	657,897	626,788	564,631	528,501
All neoplasms except respiratory cancers (*see* text-fig. C1)	89,921	92,710	92,995	93,837	94,539	91,907	91,708	91,726	94,071	96,436
Respiratory cancers	3,382	4,966	6,899	11,095	15,766	20,471	26,296	33,575	39,511	43,024
Females										
All causes except neoplasms[c]	691,566	640,736	587,619	524,603	486,660	464,038	435,145	398,603	345,983	319,529
All neoplasms except respiratory cancers (*see* text-fig. C2)	84,834	83,139	80,563	76,162	72,575	67,776	65,031	63,745	63,517	64,281
Respiratory cancers	1,473	1,872	2,354	3,050	3,078	3,090	3,551	5,020	6,894	8,672

Footnotes for tables D3, D4, and D6

[a,b,c] *See* footnotes to table D1.

[d] The standard error of a 1978 single-year rate, by the Poisson approximation, is roughly its square root (e.g., a rate of 900 would have a standard error of about ±30).

[e] These are the cancers that are strongly affected both by alcohol and by all forms of tobacco, including the pipes which men smoked in the last century (*see* sections 5.1 and 5.2). The trends in all four cancers are, not surprisingly, rather similar.

[f] Lung (including trachea and bronchus) cancer rates are affected more strongly by cigarette than by pipe smoking (*see* section 5.1), and the increases in respiratory cancer among people under 65 yr old during the past quarter century can be chiefly ascribed to prior widespread adoption of cigarette smoking. (*See* appendix E. There is no *good* evidence of any substantial increases in lung cancer death certification rates among non-smokers under 65 yr old during this period.)

[g] Cancer of the intestines may arise in the small intestine, in the ascending, transverse, descending or sigmoid colon, or in the rectum. U.S. mortality data do not seem to be sufficiently precise to allow unbiased examination of the trends for *any* of the separate parts of the intestines (*see* text), not even for "colon" and "rectum."

[h] Liver, excluding cases where cancer was merely stated to be in the liver, but including cases specified as primary cancer of the liver or of the bile ducts inside the liver.

[i] Gallbladder, including the bile ducts outside the liver.

[j] Mesentery, peritoneum, and unspecified digestive sites (the latter comprising the minority in 1948, when separate totals were last published).

[k] In middle age there are now so few deaths from non-melanoma skin cancers that the data for "total skin" represent the melanoma death rates reasonably accurately, but in old age the continuing decrease in the death rates from non-melanoma skin cancers still dilutes the progressive increase in melanoma death rates [*see* Burbank (1971)].

[l] "Other urinary organs" (ureter and urethra, in which cancers are rare) were included with "bladder" up to 1967, and were then transferred to "kidney" from 1968 onwards.

[m] Endometrium, including all cancers of unspecified parts of the uterus and hence some incompletely described cancers of the uterine cervix, especially in the earlier years.

[n] The distinction between "malignant" and "benign" is less clear-cut for brain tumors than for most other neoplasms, and so the most meaningful analysis seems to be of all fatal tumors of the central nervous system, irrespective of histology. Even here, however, large biases are possible, for in older people, symptoms due to brain tumors may be misdiagnosed as due to senility or vascular disease. Such errors, of course, are less likely for brain tumors that develop in middle age, which may account for the marked upward trend in brain tumor death *certification* rates for the old being entirely absent for people in middle age.

[o] There is considerable diagnostic uncertainty among lymphosarcoma, reticulum cell sarcoma, and various other lymphomas, so we have not attempted to examine them separately. Myeloma was also included because data on myeloma were published separately only from 1968. (Since 1968, the myeloma death *certification* rates for each sex have been increasing at 1.2%/annum among people under 65 years old and at 3.2%/annum among older people.)

[p] On many death certificates, the anatomic site of origin of the cancerous cells that killed the patient is not recorded. This means that for the various specified sites which we have listed separately, the true rates may be a few percent higher than the listed rates. In years when any distinction between "other specified" and "unspecified" sites can be made from U.S. government publications, the unspecified site death certificates greatly outnumber the specified site certificates, although the distinction between them seems surprisingly erratic (e.g., when the rates for 1957 and 1958 are compared).

TABLE D1.—*U.S. age-standardized rates[a] of death certification[b]/100 million people aged under 65 years, 1933–77*

There are at present ~100 million ♂ and 100 million ♀ under 65 years old in the United States, so the cited rates are roughly similar in magnitude to the actual annual numbers of such deaths.

The 18 age-specific death rates from non-respiratory cancer for 1933–77 and for 1973–77 are compared in text-figures C1 and C2 on page 1272.

Type of cancer	Rates[a]/100 million people, aged under 65 yr, for:									
	Earlier years[b]				More recent years					
	1933–37 (~1935)	1938–42 (~1940)	1943–47 (~1945)	1948–52 (~1950)	1953–57 (~1955)	1958–62 (~1960)	1963–67 (~1965)	1968–72 (~1970)	1973–77 (~1975)	1978 only
Males										
All causes except neoplasms[c]	784,512	675,405	598,171	505,815	448,428	435,853	433,092	423,715	370,013	338,899
All neoplasms except respiratory cancers (*see* text-fig. C1)	58,709	60,226	60,800	59,609	57,938	57,176	57,390	55,282	53,356	52,538
Respiratory cancers	5,812	8,517	11,818	15,498	19,495	23,230	26,766	30,683	32,748	33,816
Females										
All causes except neoplasms[c]	564,675	455,557	372,001	283,429	233,621	219,565	211,012	201,097	171,834	157,607
All neoplasms except respiratory cancers (*see* text-fig. C2)	90,108	87,716	84,401	77,197	71,893	68,765	66,863	63,719	60,574	58,618
Respiratory cancers	2,102	2,450	2,889	2,785	2,820	3,539	4,922	7,568	10,266	12,064

[a] There are moderate uncertainties in the Census Bureau estimates of the age/sex-specific numbers of people at risk of death in each year, especially prior to 1950. (*See* appendix A for standardization methods and appendix B for the population estimates we have used, which differ from those used by other authors.) Also, we are so uncertain as to how well, in the past or in the present, the distinction between "white" and "nonwhite" on death certificates corresponds unbiasedly with that on census returns that only "proportional mortality" analyses of race-specific data seem justifiable. We have therefore presented our analysis of absolute death rates only for all races combined, ignoring estimates of skin color.

[b] There are large uncertainties in the correctness of the *certified* causes of death, especially in the earlier years. Patients dying of cancer of one site might be miscertified as dying of cancer of some other site, or perhaps as dying of a non-cancerous cause (if, for example, the cancer caused or triggered fatal pneumonia, tuberculosis or cerebral disease). For example, in the earlier periods, secondary deposits in the lung from cancers elsewhere were sometimes miscertified as lung cancers; conversely, true primary lung cancers were often not certified as respiratory cancer. Such errors will, of course, be more common among older people, but even among people under 65 years old, the development by the early 1950's of radiology and of aseptic techniques for reasonably safe open-chest and other diagnostic and curative operations would bias the mortality trends in the early years. (It is uncertain whether there has been material progress during the past quarter century in the cure rates among people under 65 years old for the *common* cancers.) People whose age at death was unspecified are ignored in all tables of age-standardized or age-specific mortality.

[c] Benign or malignant, solid or diffuse. Age-specific death rates for Hodgkin's disease, which is nowadays considered to be a neoplasm, were estimated for the period 1939–48 as 91% (the appropriate percentage if the all-ages data for 1939–48 are aggregated) of those for all "other infectious" causes of death.

trends in mortality are downward (last column in table D3) rather than upward. The chief exceptions are pancreatic cancer in women and melanoma in both sexes.

The recent trends (expressed as the percent change per annum in the two separate age-standardized rates both under and over age 65) in the more common cancers are summarized in text-figure D1. There is a general tendency for the rates of change under age 65 to be slightly more favorable than those in old age. The tumor types that stand out most clearly from this general relationship are skin cancer in males (where the increases are much more rapid among people under age 65, unfortunately suggesting that the increases in melanoma will continue for at least the rest of this century and probably beyond) and brain tumors in both sexes (where despite falling death rates in middle age there are large increases in old age, perhaps because of progressive rectification of diagnostic errors; *see* below). Separate discussion of each of the major trends in mortality follows. Because of the methodological uncertainty (amounting to perhaps ±0.5%/yr) in the incidence trends, we do not discuss them as fully.

Mouth, pharynx, larynx, and esophagus.—These are the sites at which cancers can be caused by alcohol and by tobacco (including pipe tobacco, which men have used since the last century). Few women previously smoked pipes, which may explain why marked upward trends are evident for such cancers only in women. The combination of both alcohol and tobacco exposure seems to cause an increase in the risk of these cancers which greatly exceeds the sum of the two separate risks (*see* section 5.2). The incidence data are distorted by the inclusion in the SNCS but not in the TNCS of salivary gland tumors of "mixed" histology (which are easily cured in most cases).

Other respiratory.—Since 1968, this category has included mesothelioma of the pleura and carcinoma of the nasal sinuses, two types of cancer that can be caused by certain occupational hazards. The absolute risk is low (under 900 males and 500 females in 1978 were certified as dying of "other respiratory" cancers),

TABLE D4.—*U.S. age-standardized rates[a] of death certification[b]/10 million people aged 65 years or over, 1953–78, from various cancers or groups of cancers[c]*

There are currently ~10 million Americans of each sex aged 65 years or over, so the cited values are roughly similar in magnitude to the annual numbers of such deaths. Consequently, those 1978 single-year rates that are under 1,000 are rather unreliable.[d]

See table D1 and page 1283 for explanation of footnote letters.

Type of cancer	Patients' sex	Rates[b]/10 million people, aged 65 or over, for:						Current (1968–78) rate of change	
		1953–57 (~1955)	1958–62 (~1960)	1963–67 (~1965)	1968–72 (~1970)	1973–77 (~1975)	1978 only	Absolute change/yr	Percent change/yr
Mouth, pharynx, larynx, or esophagus[e]	♂	8,027	7,580	7,214	7,324	7,478	7,487	+24	+0.3
	♀	1,786	1,654	1,551	1,643	1,787	1,933	+30	+1.7
Trachea, bronchus, and lung[f]	♂	—	—	—	31,539	37,424	40,888	+1197	+3.4
	♀	—	—	—	4,692	6,550	8,296	+403	+6.9
Other respiratory sites (including pleura and nasal sinus)	♂	—	—	—	483	492	468	+2	+0.3
	♀	—	—	—	205	195	203	−1	−0.7
Sub-total: all respiratory sites except larynx	♂	14,277	19,016	24,823	32,022	37,916	41,356	—	—
	♀	2,937	2,981	3,442	4,897	6,745	8,499	—	—
Stomach	♂	14,368	11,827	9,552	7,708	6,519	5,892	−241	−3.4
	♀	7,547	5,930	4,635	3,667	3,047	2,870	−117	−3.5
Intestines, chiefly large intestine (colon and rectum)[g]	♂	17,916	17,749	17,761	17,958	18,265	18,839	+83	+0.5
	♀	15,502	14,672	14,024	13,497	13,256	13,437	−35	−0.3
Liver[h]	♂	—	—	—	926	957	1,067	+13	+1.3
	♀	—	—	—	364	376	395	+4	+1.0
Gallbladder and ducts[i]	♂	—	—	—	1,267	1,193	1,192	−14	−1.1
	♀	—	—	—	1,749	1,479	1,459	−48	−3.0
Sub-total: liver, gallbladder, and bile ducts	♂	1,921	2,106	2,208	2,193	2,150	2,259	—	—
	♀	2,651	2,561	2,357	2,113	1,855	1,854	—	—
Pancreas	♂	5,816	6,426	6,899	7,090	7,169	7,247	+9	+0.1
	♀	3,842	4,074	4,226	4,390	4,463	4,637	+24	+0.5
Remaining digestive sites, chiefly peritoneum[j]	♂	729	668	628	500	483	417	−7	−1.4
	♀	649	610	540	431	365	317	−13	−3.4
Bone	♂	837	617	521	502	465	436	−8	−1.7
	♀	468	359	308	286	261	244	−6	−2.2
Connective and soft tissue sarcomas	♂	228	273	323	357	353	355	+0.4	+0.1
	♀	156	184	209	243	244	273	+3	+1.1
Skin, chiefly melanoma[k]	♂	1,867	1,739	1,679	1,448	1,527	1,608	+15	+1.0
	♀	1,118	961	863	780	789	840	+7	+0.9
Breast	♀	11,356	10,633	10,351	10,603	11,087	11,070	+76	+0.7
Bladder[l]	♂	5,416	5,496	5,501	5,626	5,781	5,732	+23	+0.4
	♀	2,258	2,042	1,876	1,673	1,615	1,623	−10	−0.6
Kidney[l]	♂	1,735	1,969	2,166	2,488	2,543	2,670	+23	+0.9
	♀	1,047	1,066	1,105	1,160	1,222	1,252	+11	+0.9
Cervix uteri	♀	3,127	2,884	2,513	2,021	1,642	1,403	−73	−4.1
Endometrium[m]	♀	4,068	3,512	3,175	2,861	2,662	2,593	−38	−1.4
Ovary	♀	3,195	3,344	3,460	3,680	3,743	3,796	+20	+0.5
Prostate	♂	19,300	18,584	18,488	18,591	19,465	20,392	+183	+1.0
Other genital sites									
Malignant	♂	435	359	320	295	252	224	−9	−3.3
	♀	645	604	545	514	495	470	−5	−1.0
Possibly benign	♀	240	147	115	72	51	39	−5	−7.7
Brain or nerves, malignant or benign[n]	♂	935	1,068	1,375	1,731	2,163	2,581	+98	+4.9
	♀	596	692	857	1,187	1,522	1,862	+75	+5.4
Eye	♂	131	123	106	112	99	102	−1	−1.2
	♀	106	91	79	79	70	64	−3	−2.5
Thyroid	♂	276	251	234	232	210	217	−1	−0.6
	♀	524	450	417	372	338	310	−6	−1.7
Leukemia	♂	3,924	4,512	4,855	5,015	5,053	5,142	+12	+0.2
	♀	2,273	2,474	2,612	2,704	2,609	2,627	−12	−0.4
Hodgkin's disease	♂	626	600	626	592	468	384	−24	−4.6
	♀	388	374	397	385	296	261	−16	−4.9
All other lymphomas[o]	♂	2,701	3,303	3,900	5,126	5,787	6,266	+133	+2.4
	♀	1,849	2,227	2,634	3,470	3,894	4,184	+90	+2.4
Other specified and unspecified[p] sites	♂	8,637	7,945	8,650	8,198	9,248	9,666	+194	+2.2
	♀	7,324	6,341	6,294	6,038	6,354	6,502	+62	+1.0

TABLE D3.—*U.S. age-standardized rates[a] of death certification[b]/100 million people aged under 65 years, 1953–78, from various cancers or groups of cancers[c]*

There are currently ~100 million people of each sex under 65 years old, so the cited rates are roughly similar in magnitude to the actual annual numbers of such deaths. Consequently, the 1978 single-year rates that are under 1,000 are rather unreliable.[d]

See table D1 and page 1283 for explanation of footnote letters.

Type of cancer	Patients' sex	Rates[b]/100 million people, aged under 65 yr, for:						Current (1968–78) rate of change	
		1953–57 (≈1955)	1958–62 (≈1960)	1963–67 (≈1965)	1968–72 (≈1970)	1973–77 (≈1975)	1978 only	Absolute change/yr	Percent change/yr
Mouth, pharynx, larynx, or eosphagus[e]	♂	5,936	6,485	6,858	7,059	7,123	7,200	+8	+0.1
	♀	1,213	1,478	1,700	2,000	2,143	2,111	+25	+1.2
Trachea, bronchus, and lung[f]	♂	—	—	—	28,799	30,911	32,080	+413	+1.4
	♀	—	—	—	7,133	9,803	11,598	+554	+6.3
Other respiratory sites (including pleura and nasal sinus)	♂	—	—	—	475	447	408	−8	−1.8
	♀	—	—	—	215	192	178	−5	−2.6
Sub-total: all respiratory sites except larynx	♂	18,275	21,290	25,390	29,274	31,358	32,488	—	—
	♀	2,714	3,378	4,734	7,348	9,995	11,776	—	—
Stomach	♂	6,808	5,539	4,478	3,753	3,270	2,983	−98	−2.8
	♀	3,293	2,717	2,216	1,815	1,551	1,403	−55	−3.3
Intestines, chiefly large intestine (colon and rectum)[g]	♂	8,954	8,739	8,624	8,521	8,298	8,276	−31	−0.4
	♀	9,014	8,576	7,977	7,486	7,130	6,807	−86	−1.2
Liver[h]	♂	—	—	—	807	795	789	0	0.0
	♀	—	—	—	354	347	383	+2	+0.4
Gallbladder and ducts[i]	♂	—	—	—	535	488	487	−9	−1.7
	♀	—	—	—	712	644	625	−16	−2.4
Sub-total: liver, gallbladder, and bile ducts	♂	1,203	1,396	1,362	1,342	1,283	1,277	—	—
	♀	1,520	1,425	1,219	1,066	991	1,008	—	—
Pancreas	♂	3,984	4,336	4,536	4,464	4,267	4,148	−40	−0.9
	♀	2,210	2,363	2,459	2,482	2,598	2,618	+13	+0.5
Remaining digestive sites, chiefly peritoneum[j]	♂	465	427	404	351	283	256	−13	−4.3
	♀	414	370	330	265	212	193	−10	−4.3
Bone	♂	936	795	747	680	600	575	−14	−2.1
	♀	656	552	483	444	380	360	−11	−2.8
Connective and soft tissue sarcomas	♂	355	419	492	516	464	473	−8	−1.6
	♀	276	338	373	421	414	426	−1	−0.3
Skin, chiefly melanoma[k]	♂	1,325	1,410	1,659	1,547	1,828	1,996	+52	+3.1
	♀	916	935	1,040	1,022	1,086	1,161	+15	+1.4
Breast	♂	138	127	121	130	123	110	−2	−1.2
	♀	15,880	16,158	17,053	17,358	17,260	17,229	−16	−0.1
Bladder[l]	♂	2,066	1,919	1,810	1,658	1,538	1,386	−30	−1.9
	♀	760	676	655	547	500	455	−10	−2.0
Kidney[l]	♂	2,012	2,051	2,134	2,206	2,236	2,300	+6	+0.3
	♀	1,008	1,006	991	1,018	1,016	1,011	0	0.0
Cervix uteri	♀	7,550	6,651	5,673	4,423	3,365	2,911	−206	−5.4
Endometrium[m]	♀	4,218	3,282	2,650	2,193	1,966	1,815	−46	−2.2
Ovary	♀	5,692	5,736	5,680	5,621	5,304	5,042	−68	−1.2
Prostate	♂	2,785	2,602	2,549	2,555	2,612	2,590	+7	+0.3
Other genital sites									
Malignant	♂	854	852	837	811	729	540	−23	−3.0
	♀	356	326	291	274	246	224	−6	−2.4
Possibly benign	♀	835	444	302	173	95	53	−16	−12.2
Brain or nerves, malignant or benign[n]	♂	4,908	4,822	4,831	4,693	4,475	4,293	−47	−1.0
	♀	3,675	3,663	3,653	3,520	3,364	3,246	−35	−1.0
Eye	♂	127	120	102	92	77	70	−3	−3.4
	♀	116	106	100	82	66	58	−3	−4.2
Thyroid	♂	236	207	186	182	153	146	−5	−3.2
	♀	340	304	255	210	177	181	−6	−3.0
Leukemia	♂	4,754	4,843	4,705	4,344	4,036	3,845	−64	−1.5
	♀	3,562	3,477	3,338	3,049	2,753	2,622	−59	−2.0
Hodgkin's disease	♂	1,775	1,770	1,770	1,573	1,065	830	−95	−7.4
	♀	992	999	1,025	918	620	486	−54	−7.2
All other lymphomas[o]	♂	3,603	3,862	4,070	4,429	4,254	4,267	−24	−0.6
	♀	2,260	2,543	2,720	2,884	2,875	2,876	+1	0.0
Other specified and unspecified[p] sites	♂	5,935	5,775	6,490	5,805	6,029	6,304	+57	+1.0
	♀	5,244	4,800	4,868	4,669	4,734	4,613	−2	−0.1

TABLE D6.—*U.S. death certification rates/10 million people aged 35–44 years,[g] 1968–78, from various cancers or groups of cancers[a,b,c,d]*
There are currently ~10 million Americans of each sex aged 35–44 years.
See table D1 and page 1283 for explanation of footnote letters.

Type of cancer	Patients' sex	Rates/10 million Americans, all races, aged 35–44 yr[g] 1968–72 (~1970)	1973–77 (~1975)	1978 rate ± SE[e]	Change, 1970–78, and significance level[f]
Mouth, pharynx, larynx or esophagus[c]	♂	296	281	271±15	−25
	♀	114	103	95±9	−19*
Trachea, bronchus, and lung[d]	♂	1,446	1,347	1,232±32	−214***
	♀	601	676	698±24	+97***
Other respiratory sites	♂	38	34	35±5	−3
	♀	21	15	17±4	−4
Stomach	♂	200	188	159±11	−41**
	♀	160	122	123±10	−37**
Intestines, chiefly colon and rectum[a]	♂	437	422	426±19	−11
	♀	473	433	377±18	−96***
Liver[b,d]	♂	43	42	50±6	+7[i]
	♀	31	27	31±5	0
Gallbladder and ducts[d]	♂	27	21	21±4	−6
	♀	30	30	26±5	−4
Pancreas	♂	224	196	167±12	−57***
	♀	128	122	109±9	−19*
Remaining digestive sites, chiefly peritoneum[d]	♂	24	19	18±4	−6
	♀	23	14	20±4	−3
Bone	♂	34	35	32±5	−2
	♀	29	21	19±4	−10*
Connective and soft tissue sarcomas	♂	49	49	48±6	−1
	♀	42	39	38±6	−4
Skin, chiefly melanoma[b]	♂	222	240	284±15	+62***
	♀	175	172	169±12	−6
Breast	♂	9	9	8±3	−1
	♀	1,969	1,807	1,716±37	−253***
Bladder[d]	♂	42	35	25±5	−17**
	♀	22	20	12±3	−10**
Kidney[d]	♂	128	129	130±10	+2
	♀	68	61	60±7	−8
Cervix uteri	♀	717	530	461±19	−256***
Endometrium[m]	♀	146	109	110±10	−36***
Ovary	♀	481	400	328±16	−153***
Prostate	♂	16	15	10±3	−6*
Other genital sites					
Malignant	♂	115	98	80±8	−35***
	♀	23	19	12±3	−11**
Possibly benign	♀	42	21	12±3	−30***
Brain or nerves, malignant or benign[n]	♂	440	412	387±18	−53**
	♀	346	311	280±15	−66***
Eye	♂	5	5	3±2	−2
	♀	5	4	2±1	−3
Thyroid	♂	14	11	12±3	−2
	♀	15	12	9±3	−6*
Leukemia	♂	324	292	299±16	−25
	♀	267	245	251±14	−16
Hodgkin's disease	♂	226	154	125±10	−101***
	♀	125	83	68±7	−57***
All other lymphomas[o]	♂	329	286	305±16	−24
	♀	207	190	177±12	−30*
Other specified and unspecified[p] sites	♂	367	348	328±16	−39*
	♀	379	356	350±17	−29
Total, all sites, all histologies	♂	5,054	4,670	4,454±60	−600***
	♀	6,638	5,942	5,571±68	−1,067***

[g] Rates estimated as average of rates at 35–39 and at ages 40–44 yr.
[e] SE denotes the standard error of the 1978 rate. The standard errors of the other two rates (1968–72 and 1973–77) are both ~0.5 SE, while the standard error of the change (1968–72 to 1978) is ~1.1 SE.
[f] *, **, *** denote $P<0.1$, $P<0.01$, $P<0.001$, respectively (two-tailed test). The change was estimated by subtraction of the 1978 rate from the 1968–72 rate.
[i] The increase in liver cancer death among males aged 35–44 yr in 1978 would be of interest if real, but it is not statistically significant (62 deaths observed in 1978 vs. 52.3 expected on the basis of the 1968–77 death rates), and corresponding increases are not seen among males aged 15–34 yr nor among males aged 45–64 yr. The slightly high rate among men aged 35–44 yr in 1978 is, therefore, probably largely or wholly an artifact of chance.

TABLE D5.—*U.S. age-standardized rates of cancer registration/100 million people under 65 years, 1947–71, from the SNCS, 1947/48, and the TNCS, 1969–71*[a,b]

The trends among "whites only" and the trends among "all races" are both presented (because there has been dispute as to which should be more reliable), although the trends suggested by both are virtually identical.

Type of cancer	Patients' sex	Whites only, aged <65 yr		All races, aged <65 yr		Long-term (1947–70) rate of change, all races	
		SNCS, 1947/48	TNCS, 1969–71	SNCS, 1947/48	TNCS, 1969–71	Absolute change/yr[c]	Percent change/yr[d]
Mouth, esophagus, pharynx, and larynx	♂	21,355	17,795	21,154	18,710	−109	−0.5
	♀	5,389	5,309	5,628	5,609	−1	−0.01
Trachea, bronchus, lung, and other respiratory sites except larynx	♂	22,022	37,435	21,966	39,038	+759	+2.6
	♀	4,996	10,223	5,070	10,209	+228	+3.1
Stomach	♂	16,083	4,795	17,303	5,290	−534	−5.3
	♀	7,757	2,279	8,277	2,446	−259	−5.4
Intestines, chiefly colon and rectum	♂	25,446	20,261	24,446	20,353	−182	−0.8
	♀	24,871	17,092	24,434	17,195	−322	−1.6
Liver[e]	♂	2,969	1,321	3,120	1,613	−67	−2.9
	♀	2,046	653	2,099	666	−64	−5.1
Gallbladder and bile ducts	♂	1,100	967	1,097	966	−6	−0.6
	♀	2,485	991	2,376	1,015	−60	−3.8
Pancreas	♂	4,737	4,828	4,770	5,100	+15	+0.3
	♀	2,976	2,761	3,066	2,933	−6	−0.2
Remaining digestive sites	♂	1,375	981	1,328	1,001	−15	−1.3
	♀	1,174	953	1,146	944	−9	−0.9
Bones[e]	♂	1,959	805	2,029	822	−54	−4.0
	♀	1,687	596	1,583	579	−45	−4.5
Connective and soft tissue	♂	1,545	1,505	1,708	1,550	−7	−0.4
	♀	1,581	1,346	1,520	1,385	−6	−0.4
Skin[f]		—	—	—	—	—	—
Breast	♂	436	849	413	844	−3	−0.8
	♀	52,343	54,132	50,982	53,867	+106	+0.2
Bladder only	♂	8,626	8,784	8,134	8,448	+14	+0.2
	♀	3,410	2,507	3,667	2,399	−56	−1.9
Kidney only	♂	3,906	4,716	3,837	4,747	+40	+0.9
	♀	1,955	2,367	1,879	2,379	+22	+1.0
Cervix uteri	♀	27,751	12,740	31,231	14,245	−755	−3.5
Endometrium and uterus, site unspecified	♀	17,712	16,974	17,614	16,336	−57	−0.3
Ovary	♀	12,361	10,365	11,984	10,105	−83	−0.8
Prostate	♂	7,178	10,249	8,182	11,275	+137	+1.4
Other genital sites	♂	2,770	4,026	2,774	3,787	+45	+1.4
	♀	2,139	1,596	2,167	1,728	−20	−1.0
Brain[g]	♂	6,820	4,950	6,487	4,767	−76[g]	−1.4[g]
	♀	4,885	3,710	4,766	3,663	−49[g]	−1.2[g]
Eye[h]		—	—	—	—	—	—
Thyroid	♂	957	1,818	838	1,716	+39	+3.2
	♀	2,799	4,725	2,720	4,532	+81	+2.3
Leukemia	♂	6,206	6,315	6,143	6,181	+2	+0.03
	♀	5,156	4,001	4,791	3,952	−37	−0.9
Hodgkin's disease	♂	2,976	3,549	2,907	3,440	+24	+0.7
	♀	2,267	2,302	2,149	2,145	0	0.0
All other lymphomas	♂	5,350	6,475	5,429	6,575	+51	+0.9
	♀	3,726	4,249	3,774	4,414	+28	+0.7
Other specified and unspecified[i] sites, including eye[h]	♂	8,618	6,335	8,687	6,636	−91	−1.2
	♀	9,394	4,675	9,326	4,874	−198	−2.9
Sub-total, all respiratory sites, including larynx	♂	26,910	42,501	26,712	44,167	+776	+2.2
	♀	5,430	10,968	5,511	10,976	+243	+3.1
Sub-total, non-respiratory and unspecified sites, excluding skin	♂	125,524	105,757	126,037	108,173	−794	−0.7
	♀	195,431	155,576	196,738	156,144	−1804	−1.0

[a] Data and population estimates from PHS monograph 29 (1955) and NCI monograph 41 (1975).
[b] For details of age standardization procedure, *see* appendix A.
[c] Estimated as difference in rates divided by 22.5 yr.
[d] Estimated as 100% × difference in log, rate(s) divided by 22.5 yr.
[e] The downward trends in liver and bone cancer registration rates may be largely attributable to a progressive reduction in misdiagnosis, because these are sites to which other types of cancer commonly metastasize. (*Note* that in the TNCS, but not in the SNCS, "joints" were explicitly included with "bones."
[f] SNCS included all skin cancers while TNCS included only melanomas, so trends in skin cancer incidence cannot be estimated from a comparison of these two surveys.
[g] Non-malignant brain tumors were counted in the Second but not in the Third Survey, so the apparent decrease in brain tumors is uninformative.
[h] Tumors of the eye were not listed separately in SNCS.
[i] The decrease in this category is chiefly due to a decrease in the number of tumors of an unspecified site. This artifactual decrease (and the similar decreases in secondary tumors mis-specified as liver or bone) must imply corresponding artifactual increases (of the order of 0.1%/yr) in many of the specified sites.

certified as "colon," the most plausible interpretation of the data is that there have been no material trends in either colon or rectal cancer mortality during the past quarter of a century among males, though both the mortality and some incidence data do suggest a slight decrease in onset rates below age 65. Similar difficulties of classification affect females, and when all intestinal sites are combined total female intestinal cancer death rates have been decreasing steadily since 1950.

Liver.—The human liver is a large organ, intimately exposed to much of what is ingested and composed of cells that are capable of rapid proliferation when necessary. Moreover, most of the chemicals that have thus far been found to be carcinogenic in animal feeding experiments cause liver cancer in animals (and one in particular, aflatoxin B_1, seems capable of doing likewise in humans). It is therefore of interest to note that among Americans under age 65 liver cancer currently accounts for only 0.8% of cancer death certificates, and that no statistically significant trends in liver cancer mortality are evident during the past decade. (Human liver cancer is still rapidly fatal in almost all cases, so neither the absolute mortality rates nor the trends can have been materially affected by improvements in therapy.) The decreases in incidence (table D5) are presumably chiefly artifactual due to the improving differential diagnosis between primary and secondary liver cancer.

Gallbladder and bile ducts.—Cancers of these two sites have different causes, gallstones being an important risk factor for the gallbladder. The two sites are unfortunately not reported separately either in mortality data or in the published incidence data from the SNCS in 1947/48. They are, however, reported separately in the TNCS (1969–71), in which the sex ratios are opposite, females developing cancer of the gallbladder rather than of the bile ducts.[4]

Tables D3, D4, and D5 indicate that decreases have occurred and are continuing to occur in the aggregate of these two types of cancers and that these decreases are larger among females than among males. This finding suggests that it is probably cancer of the gallbladder that is chiefly decreasing, rather than cancer of the bile ducts. However, since, like liver cancer, both diseases are commonly fatal (with 5-yr relative survival rates <10%), the real trends in incidence and mortality must be similar. As this is not what the available data indicate, the true size of the trends remains unknown. If reliable site-specific data were available, the relative decrease in cancer of the gallbladder might be as striking as that in cancer of the stomach. We do not know whether whatever decrease does exist is partly due to a decrease of the biologic causes of the disease or whether it is due simply to progressively more surgical treatment of gallstones and to removal of more and more of those few gallbladders at greatest risk of gallstone formation.

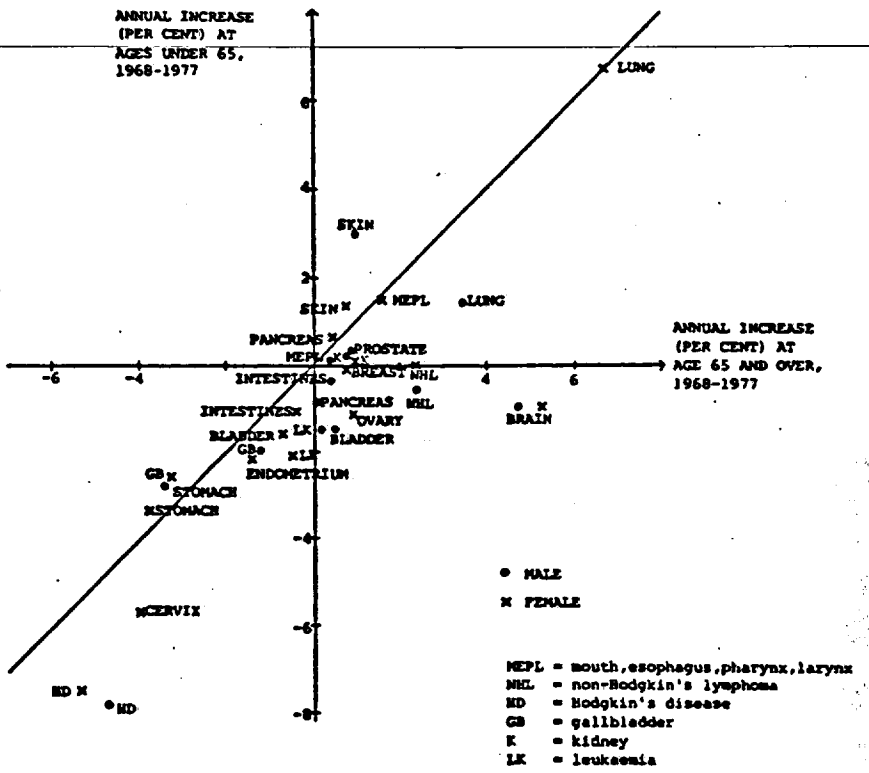
Pancreas.—It is encouraging that, after increasing for decades, the trend in male pancreatic cancer at ages under 65 is now downward, the decreases in early middle age being particularly rapid. Pancreatic cancer is again so uniformly fatal that treatment cannot have affected these trends. If the correlation of smoking with pancreatic cancer represents a cause-and-effect relationship, one might expect the ratio of rates among smokers and non-smokers to be increasing, as has been true in recent years for lung cancer. If this ratio is indeed increasing, then among middle-aged male non-smokers the trend in pancreatic cancer mortality must be even more steeply downward than these national data suggest (as might the female non-smoker rates). This prediction, and a similar prediction of steeper-than-average downward bladder cancer trends among non-smokers, could easily be checked in the data from the two large prospective studies of U.S. non-smokers.

Remaining digestive.—The decreases in this may be chiefly artifactual, due to transfer of some cancers of an unspecified digestive site either to a wholly unspecified site or to some specified site. Since 1968 "remaining digestive" has included peritoneal mesothelioma, a type of tumor that can be caused by asbestos, but these are so rare (only a few dozen per year in each sex out of a few hundred per year "remaining digestive" in each sex: Cutler and Young, 1975) that their trends cannot be estimated from the trends in "remaining digestive."

Bone.—The apparent decreases in "bone" cancer death certification rates (and incidence rates) may be due chiefly to the progressive elimination of misdiagnosed secondaries (Boyd et al., 1969), though the similar magnitudes of the trends in young and old does not support this.

Skin.—The upward trends in skin cancer mortality during 1950–67 were the sum of an increasing death rate from melanomas, together with a decreasing death rate from other skin tumors (Burbank, 1970). The increases are most rapid in middle age, and so the rates in old age will probably increase even more rapidly in future decades than is already the case. The causes of melanoma are not well understood; exposure to sunlight seems to be involved, and patients with xeroderma pigmentosum, which involves a genetic deficiency in their ability to repair the damage done to their DNA by sunlight, are at extraordinarily high risk of melanoma (Robbins et al., 1974). However, people whose work involves regular outdoor exposure seem paradoxically to be at lower risk of melanoma than otherwise similar people who work indoors (Lee and Strickland, 1980), perhaps because a permanent suntan is protective. Therefore, the conditions that maximize risk may be those that involve sudden exposure of untanned skin to sunlight. It is possible that the worldwide increases in melanoma are due merely to some change in the pattern of human exposure to sunlight (e.g., changes in clothing or increases in

[4] At ages <65 in 1969–71, the all-races age-standardized incidence rates per 100 million for cancer of the gallbladder were 573 for females and 305 for males, whereas for cancer of the extrahepatic bile ducts they were 442 for females and 661 for males.



TEXT-FIGURE D1.—Trends in U.S. cancer death certification rates for cancers that are common in middle or old age: Relationship between trends above and below age 65 years.

and it is striking that it shows no upward trend. This may be partly because the trends in pleural and nasal sinus cancers are opposite in direction and cancel each other out (Burbank, 1970) and partly because of a progressive tendency for doctors to avoid such imprecise terms as cancer of the "mediastinum" or "thoracic organs" in death certification. (In Britain, where a more detailed subdivision of these "other respiratory" cancers is published, the percentage of the small number of male "other respiratory" cancers that were pleural increased from 36% in 1968-72 to 56% in 1978, whereas the percentage that were mediastinal decreased from 12 to 5%.)

Stomach.—Stomach cancer is now decreasing throughout the developed world (table 5 on page 1202), even though the case fatality rate is still about 90%. None of the dietary explanations involving reductions in contamination by micro-organisms of food due to modern food processing or storage have been either accepted or rejected, possibly because it is the diet during childhood or early adult life that largely determines the risk in middle or old age, an association that would be difficult to study epidemiologically. The enormously encouraging feature of the U.S. stomach cancer trends is that they are continuing downward in each age group *throughout middle age*, which strongly suggests that the decreases occurring in old age will continue throughout this century and perhaps beyond. The United States, which used to have very high stomach cancer rates, already has incidence rates that are among the lowest recorded in any country in the world, and hopefully the decreases in the United States will be a model that other countries will continue to follow.

Intestines.—On death certificates, intestinal cancer may be of either a specified or an unspecified part of the intestines. In 1958, about two-thirds of male intestinal cancer deaths were certified as being of some *specified*[3] intestinal site, and one-third were of an *unspecified* intestinal site, whereas by 1977 the converse was true. Overall, little change occurred in total male intestinal cancer mortality during this period. Clearly, although the male death certification rates for each specific intestinal site have been approximately halved, these decreases cannot be accepted as real because the unspecified site rates have doubled. However, it has been traditional to present the data for one particular specific site ("rectum," comprising the last foot or so of the large intestine) separately and to describe the remainder, including unspecified intestinal sites, as "colon." This approach gives the misleading impression that rectal cancer rates are really decreasing and colon cancer rates are really increasing, whereas in fact the decreases in the death certification rates for rectum are, if anything, slightly less extreme than for many of the other (colonic) specified parts of the intestines. In view of the fact that half of all fatal cancers diagnosed in hospital as "rectum" in the TNCS were eventually

[3] Small intestine, ascending colon, transverse colon, descending colon, sigmoid colon, or rectum.

estimation of separate trends in the various different types of leukemia is, unfortunately, not possible from the available data due to lack of consistent classification and terminology. The lack of any net trend in either direction in leukemia mortality among older people may represent a balance between increasingly thorough diagnosis among elderly patients who are dying of leukemia and slightly better treatment of the disease. It is not possible in this situation to know whether the underlying age-specific leukemia onset rates are changing, but the incidence data do suggest that some decreases in real onset rates are in progress, at least among females.

All other tumors of the reticuloendothelial system.—These tumors comprise several different diseases, none of which (except possibly myeloma) can be studied separately, again because of a lack of consistent diagnostic criteria. Among people under age 65, for whom no net trends in mortality are evident, rising incidence may be balanced by better treatment; or perhaps no material trends exist in lymphoma onset rates, but (as for leukemia) better case ascertainment is being balanced by better treatment.

Death certification rates from myelomatosis have been rising steadily during 1968–78 (1.2±0.3%/year among people under age 65 and 3.2±0.2%/year among older people). This difference between the rates of increase in middle and in old age might be the tail end of the sort of "successive generation effect" described for smoking and lung cancer in appendix E. Alternatively, it might simply mean that the apparent increase in myelomatosis is largely or wholly due merely to improved case finding rather than to increased incidence, because improved case finding must have occurred during 1968–78 and might be expected to have its greatest effect among the old. (Recent improvements in diagnostic technology could cause particularly large upward biases in myeloma death certification rates, because the disease may present acutely as terminal renal failure or bone marrow failure, and the correct diagnosis could easily be missed if electrophoretic blood protein analyses are not undertaken.)

Other and unspecified sites.—Of all cancers at ages under 65, 6–8% are of an unspecified site, the exact percentage varying irregularly since 1950, with, rather surprisingly, slight increases during the past decade.

"Early" and "Late"-Acting Determinants of Cancer: The Crucial Importance of Trends in Cancer in Early Middle Age

The different trends in the death certification rates for each separate type of cancer have a variety of different causes, and each must therefore be discussed separately. Some general points can, however, be made about the surprisingly long delays that typically seem to exist between cause and effect in carcinogenesis. For many types of cancer the cancerous alteration of a normal cell is thought to involve the accumulation, over several decades, of at least two different sorts of permanent, or semi-permanent, change in particular cells, such that it is only a cell that has suffered the "early" change(s) that is at risk of the "late" change(s) that will finally convert it into the seed of a growing cancer. (For review, *see* Peto, 1977.) If this theory, or anything roughly equivalent to it, is true, then the determinants of cancer can perhaps be divided into three main classes: *a*) those that principally affect only the "early" stages, *b*) those that principally affect only the "late" stages, and *c*) those that have a substantial effect on both early and late stages. Theoretically, tripling the likelihood of the early stages occurring triples the risk of cancer, as does tripling (among cells that have already undergone their "early" changes) the likelihood of the late stages occurring, whereas doing both might increase the final risk of cancer ninefold.

Again, whether or not this is exactly true, the risk of cancer in old age is strongly dependent both on the rate of occurrence of the "early" changes in one's cells during childhood or early adult life, and on the rate of occurrence, among cells that have undergone the early change(s), of the "late" change(s) in middle or old age. Clearly, if the early changes are increased or decreased then it may be 50 years or more before the full effects of this on national mortality data are evident, whereas if the later stages are increased (e.g., by post-menopausal hormones) or decreased (e.g., by stopping smoking, since smoking seems to affect both the early and the late stages of lung carcinogenesis—*see* appendix E) then measurable effects may be seen within a decade.

If there were no general upward trend in current cancer onset rates, this would suggest that recent changes in the American life-style or environment have not grossly affected the "later" processes of induction of most cancers, but it would not offer any guarantee against significant increases or decreases during the past quarter of a century in the rates of occurrence of the "early" stages. However, separate examination of the trends in mortality among adults in *early* middle age might reveal more clearly any adverse or beneficial tendencies in exposure to early-stage carcinogens. We have therefore tabulated separately the trends in cancer death rates observed during the 1970's among Americans aged 35–44 (table D6). The absolute numbers of deaths involved are very small, which introduces difficulties of statistical significance that did not affect the earlier tables. However, where statistically significant trends in one or another direction can be demonstrated among people currently aged 35–44, the directions of these significant trends are of crucial importance, because they offer some of the best clues there are as to the likely direction of the trends in cancer mortality that will be seen in the 1980's among people aged 45–54, in the 1990's among people aged 55–64, and among old people early in the next century.

The significant patterns in table D6 seem to be:

a) Continuation at ages 35–44 of the *upward* trends already noted above among older people in cancer of the lung (females only) and skin (males only).

b) Continuation at ages 35–44 of the *downward*

sunbathing), particularly since the chief increases seem to be in melanoma of the trunk and legs rather than of the face (Magnus, 1980). However, melanocytes are also subject to hormonal influences, and it could yet be that other, undiscovered, causes are also important.

Breast.—The lack of any substantial trends in breast cancer incidence or mortality at ages under 65 is deceptive and conceals various smaller fluctuations in mortality in particular age groups, with women born in different decades having differing risks in later life. Delay of first pregnancy is known to be a determinant of breast cancer risk in later life (MacMahon et al., 1973), and Blot (1980) has argued that the reproductive patterns of different cohorts of American women can account for some or all of the small fluctuations in breast cancer death rates in particular cohorts of women. (Women who were young during the Great Depression of the 1930's had their children at a somewhat delayed time, and their breast cancer mortality nowadays is slightly increased, while women who were young in the postwar baby boom now have, in early middle age, substantially decreased breast cancer rates because of their early pregnancies.)

Bladder.—The steady decrease in bladder cancer death rates in both sexes is encouraging, since bladder cancer can be caused by occupational exposure to various carcinogens. [Blot and Fraumeni (1975) report similar decreases in the industrial Northeast of the United States, despite a heavy concentration of chemical manufacturing industries there.] However, the discrepancy between rising incidence and falling mortality is more marked for bladder than for any other type of cancer except thyroid cancer (*see* below). This divergence may be contributed to by improvements in treatment, but the reason why it is peculiarly extreme is probably because there is no sharp distinction between bladder "papillomas" and bladder "carcinomas," and by now a substantial proportion of the bladder "cancers" counted by certain registries are what clinicians or histologists in the past might have classified as "papillomas" (Muir, 1976).

Kidney.—At ages under 65, small increases in male (but, until recently, not female) kidney cancer death certification rates have been continuing for 25 years, together with slightly larger increases in incidence in both sexes. Men who smoke cigarettes have mutagenic urine (Yamasaki and Ames, 1977), a marked excess of bladder cancer (*see* section 5.1), and about a 40% excess of kidney cancer in both of the large American prospective studies. It is not known whether this excess is an artifact of the epidemiologic method, but if not then it could account for the small upward trend in mortality from cancer of the kidney.

Cervix, endometrium, and ovary.—Large decreases in mortality from cancer of the uterine cervix have continued throughout the past half century at least, were apparent long before screening for cancer of the cervix became widespread, and are the chief reason for the large, steady decrease in female non-respiratory death rates over the past 40 years. The causes of this substantial improvement are not fully understood, though effects of improved personal hygiene may be relevant. It is not known what the current trends in cervix cancer mortality would be were it not for the benefits of cervical cancer screening programs. Also, if all of the deaths between 1933 and 1978 from cancer of the cervix that were certified merely as being due to "cancer of the uterus" (with the exact site not otherwise specified) could be transferred from "endometrium," where they now are, to "cervix," the downward trend in cancer of the cervix would presumably be much steeper and that from cancer of the endometrium much shallower. This suggestion is supported by the trends in recorded incidence in table D5. Finally, an increasing percentage of American women in middle and old age, when cancer is most common, have already undergone hysterectomy for various reasons, thereby removing both cervix uteri and endometrium (and, sometimes, both ovaries) from risk. A better statistic might be the death rate from such cancers per uterus, not per woman (and, likewise, in ovarian cancer per ovary), and the recent trends in these rates would presumably seem somewhat less encouraging. They might well indicate no material decrease in cancer of the endometrium, though the decreases in cancer of the cervix seem far too large to be accounted for by any combination of the above sources of error.

Brain.—The distinction between malignant brain tumors, benign brain tumors, and brain tumors of unspecified malignancy is not reliable, and so all three must be pooled if meaningful analyses, especially of trends, are to emerge. Because of the possibility of diagnostic confusion between brain tumors and other brain diseases in old people, separate examination of the death rates among people under age 65 and those among older people is perhaps more important for brain tumors than for any other category of neoplasm (text-fig. D1). Under age 65, we see a 1% per annum decrease in brain tumor death certification rates. Over age 65 the opposite is true, and a very rapid increase in death certification rates exists, possibly due to a steady improvement of diagnostic standards. Future death certification and, particularly, registered incidence rates may be further increased as the diagnostic accuracy conferred by computerized transaxial tomograms ("EMI-scans") and other special investigations becomes more and more widely available.

Thyroid.—The contrast between steadily falling death certification rates and the outstandingly rapid increase in incidence suggested by table D5 is greater for thyroid cancer than for any other type of tumor and may in part be explained by the epidemic of non-fatal thyroid cancers induced by medical use of X-rays.

Hodgkin's disease and certain forms of leukemia.—These diseases are much more treatable now than they were a decade or two ago. This alone will produce substantial downward trends in mortality, especially among younger people (*see* table C2), and may perhaps have encouraged more thorough efforts at correct diagnosis, especially among older people. Reliable

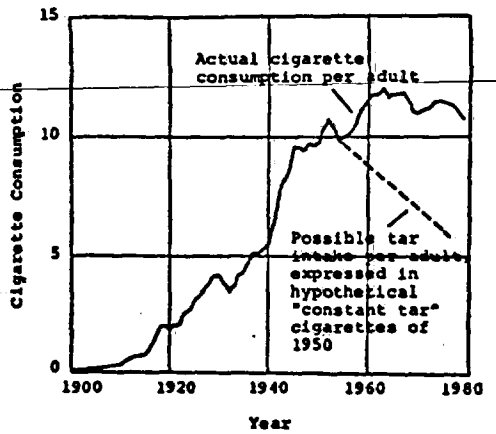
so there is no reason to distrust the importance of early exposure which is apparent in the uncontrolled human data. The human data in text-figure E1 deserve careful examination, because it is impossible to interpret properly the recent lung cancer trends in any developed country unless one appreciates the crucial importance of cigarette smoking in *early* life (as well as the importance of more recent exposure, of course).

Thus lung cancer risks at age 60 years certainly depend very strongly on cigarette usage both at ages 15–25 and at ages over 45. Presumably, they also depend to some extent on cigarette usage at ages 25–45, though the strength of this dependence is not known. Therefore, to interpret in any detail the lung cancer rates among people of a particular age, we ideally need to know not only what they have been smoking in the recent past but also what they smoked decades ago in their teens or twenties. Moreover, to interpret recent lung cancer *trends* among people of a given age, we ideally need to know not only the recent *trends* in adult cigarette consumption but also the *trends* in cigarette consumption by teenagers or young adults in the distant past.

Trends in U.S. Smoking and Lung Cancer

Unfortunately, of course, the exact smoking habits of the young in the distant past are not known. Estimates of varying degrees of reliability have been made, but none can be accepted with confidence, and we prefer to base our inferences chiefly on the total sales of manufactured cigarettes, which should be reasonably reliably known,[1] together with the observation (Surgeon General, 1980) that female cigarette usage seemed to lag about 25 or 30 years behind male cigarette usage.

The major changes in American smoking habits in this century have been the rise in cigarette usage (text-fig. E2) in the first half of the century and the subsequent halving of tar yields per cigarette (Owen, 1976). One cannot, of course, predict from these crude total sales data the exact relative risks of different generations, because neither the ages of the people who smoked the cigarettes sold in past years nor the "style" in which they smoked their cigarettes is known.[2]



TEXT-FIGURE E2.—Mean daily sales of manufactured cigarettes per U.S. adult over 18 years of age (Surgeon General, 1980), together with a crude estimate of tar yield per adult, based on Owen, 1976. *The estimate of tar yield allows approximately for decreases since 1954 in tar yield per cigarette smoked in a standard manner (but not for any hypothetical compensatory increases in number of puffs per low-nicotine cigarette).*

Moreover, if dietary factors affect lung cancer (*see* section 5.3) these too may change with time. Therefore, there seems little point in trying to devise complex mathematical predictive formulas based on detailed models. Instead, we shall exemplify the qualitative ways in which trends in tobacco exposure might be the chief determinants of the lung cancer trends by a detailed discussion of one particular comparison—that between the lung cancer rates of men aged 45–49 in 1937, 1957, and 1977.

Example: Trends in lung cancer mortality among U.S. males aged 45–49, as we go from 1937, to 1957, to 1977.—Men aged 45–49 in 1937: These men were born in about 1890, and because they grew up before World War I (which ended in 1918) very *few* of them smoked substantial numbers of manufactured cigarettes regularly from early adult life (text-fig. E2). However, *many* will have smoked pipes and/or cigars (which both confer some risk of lung cancer, though not nearly as large a risk as do cigarettes), and a few may have smoked hand-rolled cigarettes.

Men aged 45–49 in 1957: These men were born in about 1910, and because they grew up between the two wars, when the average usage of manufactured cigarettes was 3 or 4/adult/day (text-fig. E2), *some* of them smoked substantial numbers of cigarettes regularly from early adult life, whereas *some* then smoked pipes and/or cigars. However, compared with the cigarettes already being used by young men between the wars, these other forms of tobacco may, by the 1930's, have had a relatively unimportant added effect on the young men's future lung cancer risks. (When a new habit, such as the use of marijuana in recent years, is in the process of being adopted by a country, it tends to be the young adults who adopt it most vigorously.)

Men aged 45–49 in 1977: These men were born in about 1930, and because they grew up after World War II (which ended in 1945), when the average cigarette

[1] Questionnaires seeking recall of quantitative smoking habits in the distant past are notoriously unreliable, and even questionnaires about current habits may be subject to large errors. For example, data from four large questionnaire-based surveys (1964, 1966, 1970, 1975) suggest about a 15% reduction between 1964 and 1975 in the number of cigarettes smoked per U.S. adult, but this reduction is probably chiefly due to progressive increases in underreporting (Warner, 1978), because no such large trends are evident in the more reliable data on the numbers of cigarettes actually manufactured. By 1975, 50% more cigarettes were being sold than the questionnaire surveys indicated were being smoked.

[2] The "style" includes stub length, puff frequency, puff size, depth of inhalation, and possibly even speed of inhalation, since this may affect the net exposure of the walls of the large upper airways (which are the part of the lung at greatest risk of cancer) to the carcinogen-carrying droplets or gases in cigarette smoke.

trends already noted above among older people in cancer of the stomach (both sexes), intestines (females only), ovary, endometrium, cervix uteri and other parts of the female reproductive system, brain (both sexes), bladder (both sexes), and in Hodgkin's disease (both sexes). The decrease in Hodgkin's disease is largely or wholly ascribable to effective treatment, but this seems unlikely to be true on the whole of these other significant decreases.

c) Recent emergence of very marked decreases in mortality at ages 35–44 from cancer of the male lung, female breast, and pancreas (chiefly in men, but perhaps also in women). At least two of these three trends are very encouraging. The decrease in male lung cancer is encouraging because it suggests that a peak in the still-evolving epidemic of male lung cancer can now be foreseen. (*See* text-fig. E3 on page 0000 for more detail; in appendix E the decrease in lung cancer mortality among younger men is attributed more to decreasing tar yields than to decreasing cigarette consumption.) The decrease in male (and perhaps female) pancreatic cancer might also be at least in part due to decreases in exposure to the affects of tobacco (*see* section 5.1) if smoking effects chiefly the *later* stages of pancreatic cancer induction. Pancreatic cancer remains almost wholly incurable, yet peak rates for cancer of the pancreas among middle-aged males were reached in the mid-1960's. Since then, decreases have occurred throughout middle age, but most especially in early middle age for which unexplained decreases of about 30% have already been recorded. The marked decrease in mortality at ages 35–44 from cancer of the female breast is perhaps less encouraging, for it may merely indicate a protective effect of early pregnancy only on the mothers of the postwar baby boom (Blot, 1980), in which case the decreases seen in table D6 will presumably be replaced in a decade or two by increases in breast cancer in early middle age due to the delayed fertility of the 1960's and 1970's.

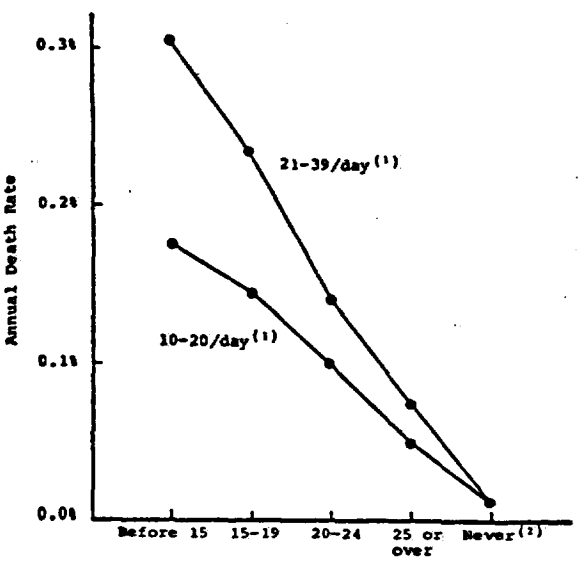
When one considers the aggregate of all types of cancer at ages 35–44, male death rates decreased by 12% between 1970 and 1978, whereas female rates decreased by 16%. These decreases are produced by the sum of many factors, but even if the effects of any "one-off" improvements in cancer therapy (and any temporary effects of the postwar baby boom) are allowed for, the net trends would still seem favorable. It is therefore reasonable to hope that the overall decreases seen during the 1970's in cancer death rates among Americans aged 35–44 will be seen at older ages around the turn of the century. The trends in lung cancer are discussed more fully in appendix E.

APPENDIX E: TRENDS IN LUNG CANCER DEATH RATES IN RELATION TO CIGARETTE USAGE AND TAR YIELDS

Effects of Smoking In Early and Recent Adult Life

As would be expected, lung cancer risks at 60 years of age depend strongly on the degree of exposure of the lungs to cigarette smoke over the previous decade or so. The chief evidence for this assertion is that *a*) people aged 60 who have given up smoking 10 years previously have lung cancer risks that are well under half the risks among continuing cigarette smokers (Rogot and Murray, 1980; Doll and Peto, 1976; Hammond, 1966) and that *b*) people who have switched to low-tar or to filter cigarettes seem to have, as a consequence, lower lung cancer risks per cigarette (Hammond et al., 1977; Wynder et al., 1976).

Perhaps more surprisingly, lung cancer risks at 60 years of age also depend strongly on the degree of exposure of the lungs to cigarette smoke during the first decade or so of adult life (text-fig. E1). The strength of the dependence (among continuing cigarette smokers) of lung cancer risks in old age on cigarette smoking habits in *early* adult life means that lung cancer rates among people in their sixties during the 1970's are strongly influenced by the smoking habits in about 1930 of the teenagers and people in their early twenties, a delay of about half a century. It also means that the trends of half a century ago in cigarette usage by young adults will be important determinants of current trends in lung cancer among old people. Analogous large effects of exposure in early "adult" life on cancer risks in later life are also seen in controlled experiments involving the regular application of one of the cancer-causing components of cigarette smoke to laboratory mice (Peto et al., 1975).



TEXT-FIGURE E1.—Data on U.S. veterans (Kahn, 1966). Lung cancer mortality at ages 55–64 among current smokers of cigarettes only, in relation to the age when cigarette smoking first began (though this was perhaps not when regular consumption of substantial numbers of cigarettes first began).

(1) *The figures 10–20 and 21–39/day refer to the maximum rate at which the subject ever normally smoked cigarettes; the lifelong average may, of course, be much less than this.*

(2) *Subject may previously have smoked "once in a while but not every day."*

in early adult life, but conversely it is an oversimplification to imagine that what happens in the age range 15–25 is the sole determinant of the predispositions that are imprinted on successive generations.

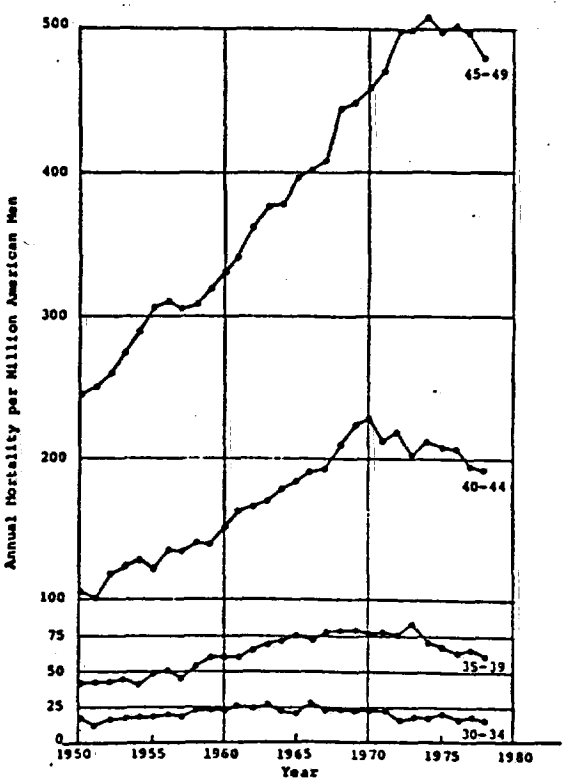
The midcentury peak in tar intake per young male.—Lacking objective data, we shall assume that the net exposure of young men to cigarette smoke during 1900–50 was, very roughly, proportional to the cigarette consumption per adult indicated by the left half of text-figure E2 and that after 1950 it was roughly proportional to the tar yield per adult indicated by the *broken line* in the right half of this graph. There are many possible sources of bias in this approximation,[4] but some may cancel each other out.

Our main conclusion, however, is that among young American men there must have been a fairly sharp peak in net exposure to cigarette smoke around the middle of the century (probably occurring at some time between 1945 and 1955, depending on trends in consumption by the young and on exactly when tar yields first began to drop rapidly) with a substantial decrease thereafter from the mid-century peak values.

Steady increase in tar intake per young female.—The Surgeon General (1980) has suggested that female smoking has lagged about 25 or 30 years behind male cigarette smoking. If the left half of text-figure E2 is shifted to the right by a quarter of a century, it suggests negligible cigarette usage by females in the 1920's, with steady increases thereafter, at least to the mid-1960's. (This is borne out by estimates of the percentages of women who smoked cigarettes, which continue to increase rapidly up to the 1960's.) The tar intake per young female must therefore have risen rapidly up to the 1950's,[5] and although it may have continued to rise thereafter (or may have flattened out thereafter), it can hardly have decreased much, at least during 1955–75. (For example, the proportion of females aged 15–16 who smoked cigarettes rose from 10% in 1968 to 20% in 1974: Surgeon General, 1980.)

Decreasing tar intake per mature adult in recent decades.—To make sense of the post-1950 lung cancer trends, we needed some estimate of the tar intake per *young* adult throughout the century (*see* above), together with some estimate of the tar intake per mature adult since World War II ended in 1945. For mature males, tar intake must have been roughly constant for a time and then decreased with decreasing tar levels. For mature females, tar intake must have risen to a maximum at some time between 1945 and 1965 and then likewise decreased.

Male lung cancer data.—From the foregoing crude estimates of trends over previous decades in tar intake by young and by mature males, one might expect lung cancer rates among older males still to be rising, since the increases in smoking by young males before World War II outweigh the decreases in tar yields among mature males in recent decades. Although the generations of men born in 1910, 1920, and 1930 all passed through the sharp "mid-century peak" of tar intake (the generation of 1930 doing so at ages 15–25), the generations born in 1940 and 1950 missed it. Therefore, although one cannot predict from the tobacco data alone whether the male generation of 1920 or the male generation of 1930 will be at greatest risk, the male generations born after 1930 should be at successively lower risk. This is indeed so (table E1, text-fig. E3), and



TEXT-FIGURE E3.—Trends since 1950 in lung cancer mortality in U.S. males at young ages; recent decreases are shown for the age groups 30–34, 35–39, 40–44, and 45–49 years.

[4] One large source of bias is that, if they have enough money to indulge their inclinations, young men are more inclined than other adults are to be at the forefront of adoption of a habit such as cigarette smoking while it is spreading, especially in or after prolonged wars. This tendency would increase the consumption per young male in the early years relative to text-fig. E2 (except that America was not very heavily involved in World War I, and that before 1945 the young did not have much spare money). Another large source of bias is that between 1920 and 1970 female smoking has been increasing fairly steadily, which again would increase the consumption per young male in the early years relative to text-fig. E2 and would make the decrease in exposure per young male since 1950 even steeper than it seems in the *broken line* in the text-figure. Finally, changes in the style of smoking (e.g., stub length, puff frequency, puff size, and speed and depth of inhalation) may bias trends in tar exposure among young men quite substantially, but in ways that are impossible to document (except that some compensation for the recent decreases in nicotine and tar seems likely).

[5] The rise will be even larger than might be anticipated just from changes in the composition and numbers of cigarettes that women smoke if American women resemble British women in having also increased the vigor with which they smoke individual cigarettes (Doll et al., 1980).

usage was about 10/adult/day (text-fig. E2), *many* of them smoked substantial numbers of cigarettes regularly from early adult life, while probably by then relatively *few* of them smoked much pipe or cigar tobacco; for the inevitable tendency of the young to be in the forefront of new drug usage seems likely to be accentuated by the disruption of their habits and values that follows a long war with widespread military conscription. (A possible analogy might be with the recent Vietnam War, which may have particularly affected the use of marijuana and other drugs by *young* adults.)

If these three successive generations of men (born 1890, 1910, and 1930) had subsequently all smoked similarly from the age of 25 or 30 onward, one might have expected excess lung cancer risks at ages 45–49 in approximate proportion to the exposure of their lungs to the carcinogenic agents in tobacco smoke in early adult life (text-fig. E1), but, of course, they were not similarly exposed in later life. The men born in 1890 had their "later life" between the wars (when the national average was still only 3 or 4 cigarettes/adult/day plus still some pipe and cigar tobacco), the men born in 1910 had their later life after World War II (when the average was 10 cigarettes/adult/day), and the men born in 1930 had their later life in the 1960's and 1970's [when the average cigarette consumption per adult had not changed much further but the tar yield per cigarette smoked under standard laboratory conditions had decreased by about half (Owen, 1976), which presumably reduces the human tar yield per cigarette by some worthwhile amount (Wald et al., 1980b) and seems to reduce the lung cancer risk per cigarette (Wynder et al., 1976; Hammond et al., 1977)].

From these data on consumption, one might expect approximately a doubling of risk at ages 45–49 between the successive generations born in 1910 and 1930, because *a*) between the times when they were both young adults there was about a threefold increase in cigarette usage per adult with no large change in tar delivery per cigarette, but *b*) between the times when they were both aged about 40 years there was a large decrease (perhaps by about one-third) in the human tar yield per cigarette with no large change in cigarette usage.

The magnitude of the increase in risk between the generations born in 1890 and in 1910 is more difficult to predict because of uncertainty as to how much *young* adults smoked as well as the uncertainty in the relative contributions of pipes, cigars, and cigarettes. If hypothetical effects of hypothetical improvements in nutritional status are ignored, one might approximately expect a fourfold increase due to perhaps a doubling of net exposure of the lungs to carcinogens in early life and perhaps a doubling of net exposure in later life.

Having discussed at length what lung cancer changes we might *expect* to see, we shall now discuss what we *do* see. Among American non-smokers aged 45–49, the annual lung cancer death rate per million men is about 50 (Hammond, 1966). Among all U.S. males aged 45–49, the lung cancer death rates per million were 150 in 1937, 300 in 1957, and 500 in 1977, in round numbers.[3] Therefore, the excess risks ascribable to tobacco were probably about 100, 250 and 450. These figures are reasonably compatible with our crude predictions (of a fourfold increase and then a twofold increase) based on the cigarette consumption data. Note particularly that, comparing 1957 with 1977, the net increase in lung cancer is composed of an increase in young people's smoking long ago, between 1930 and 1950, and a more recent decrease in tar yields, between the 1950's and the 1970's. (Looking further ahead, during the 1980's there should be a worthwhile decrease in the U.S. lung cancer death rates among men aged 45–49. This predicted decrease involves comparison of men born about 1930 with men born about 1940, and the ones born around 1940 should have been exposed to substantially lower net tar deliveries either at ages 15–30, or at ages 30–45, or both.)

Terminology: The "successive generation effect."— Because we were examining a middle-aged group of men (aged 45–49 yr), there was a delay of some 30 years between cause (in the form of trends in teenage cigarette use) and full effect, but if we had been examining older men (e.g., aged 65–69 years), there would have been an even longer delay (≈50 yr) between cause and full effect. These long delays are sometimes described in terms of a "latent period," but this terminology may misleadingly suggest a fixed delay (e.g., of 30 yr) between cause and effect. The reality is more complex, of course, and it is perhaps preferable to speak of a "successive generation effect," whereby the risks among successive generations of men are directly dependent not only on their recent smoking habits (i.e., over the past decade or so) but also on the predisposition to lung cancer which has been imprinted on them by their smoking habits in the distant past. The "successive generation effect" and recent smoking habits *together* determine current lung cancer risks, and neither should be ignored. (For example, if the "successive generation effect" were ignored, one might mistakenly predict a decrease in male lung cancer at ages 45–49 between 1957 and 1977 due to the decrease in tar yields, whereas in fact an increase should be expected.)

Note that although we have emphasized chiefly the importance of cigarette smoking in very early life (i.e., at ages 15–25 or so), in imprinting various different predispositions to subsequent lung cancer on successive generations of men, the amounts smoked at 25–35 (and possibly even at 35–45) must also be of some importance. It is obviously very wrong to ignore exposure

[3] The death certification rates were 127, 305, and 497 (table E1 on page 1296), and in table E2 (*see* below) we shall suggest that the 1937 lung cancer death certification rate for people aged 45–49 may have been between 71 and 87% of the true 1937 lung cancer death rate.

TABLE E2.—*Approximate undercertification factors during 1933–52*[a,b,c]

Age, yr	Estimated undercertification for:			
	1933–37	1938–42	1943–47	1948–52
40–44 (and younger)	0.86	0.93	1.00	1.00
45–49	0.71	0.87	1.00	1.00
50–54	0.69	0.84	1.00	1.00
55–59	0.72	0.86	1.00	1.00
60–64	0.64	0.80	0.97	1.00
65–69	0.57	0.75	0.89	1.00
70–74	0.52	0.63	0.84	1.00

[a] The undercertification factor is here defined as the ratio of the recorded to the true lung cancer death rate. This table lists the undercertification factors indicated in years 1933–37, 1938–42, and 1943–47 if ♀ death certification rates in 1948–52 were about right, and ♀ rates in earlier quinquennia differed from the 1948–52 rates because of undercertification.

[b] What would ideally be required would be separate estimates of the probabilities that ♀ lung cancer will be correctly certified, and that ♀ non-lung cancer will be miscertified as lung cancer. These two ideal probabilities might carry over more accurately to the ♂ data than the above single undercertification factors do.

[c] The contemporary degree of undercertification in England and Wales might be roughly similar, so in correcting British rates for 1941–45 we have used the simple average of these U.S. correction factors for 1938–42 and 1943–47.

TABLE E3.—*Estimated true male U.S. lung cancer death rates in years 1933–52*[a]

Age, yr	Estimated true U.S. mortality rates/million people, for:			
	1933–37	1938–42	1943–47	1948–52[b]
30–34	14	16	17	17
35–39	30	33	39	44
40–44	65	78	94	107
45–49	142	176	187	246
50–54	230	289	353	467
55–59	293	403	542	739
60–64	370	510	661	969
65–69[c]	428	556	708	1,052
70–74[c]	452	600	700	1,032
75–79[d]	—	—	—	—
80–84[d]	—	—	—	—
85+[d]	—	—	—	—

[a] These are the ♂ mortality rates that would be obtained if the undercertification factors indicated by the ♀ trends during this period (table E2) are applied to the ♂ lung cancer death certification rates/million people.

[b] Actual ♂ rates, because correction factors for 1948–52 are all 1.00.

[c] Less reliable than rates in middle age.

[d] Too unreliable for any useful estimation to be possible.

TABLE E4.—*Mortality in England and Wales from cancer of the lung, estimated as all respiratory, excluding larynx*[a,b]

Age, yr	Sex	Annual death certification rates/million people, for:							
		1942–45[c] (~1943)	1946–50[c] (~1948)	1951–55 (~1953)	1956–60 (~1958)	1961–65 (~1963)	1966–70 (~1968)	1971–75 (~1973)	1976–79 (1/1/1978)
30–34	♂	39 (40)	41 (41)	38	37	33	25	24	17
	♀	14 (15)	15 (15)	16	15	11	12	9	8
35–39	♂	87 (90)	97 (97)	101	95	92	77	58	56
	♀	25 (26)	27 (27)	30	33	33	32	26	23
40–44	♂	203 (210)	242 (242)	253	256	228	220	177	137
	♀	39 (40)	51 (51)	54	63	71	84	68	62
45–49	♂	404 (432)	555 (555)	589	597	570	537	506	400
	♀	63 (67)	77 (77)	92	108	140	161	183	163
50–54	♂	626 (680)	972 (972)	1,242	1,260	1,234	1,172	1,075	1,019
	♀	102 (111)	123 (123)	144	175	224	290	331	359
55–59	♂	924 (994)	1,375 (1,375)	2,033	2,338	2,299	2,219	2,085	1,891
	♀	135 (145)	176 (176)	214	248	315	409	500	551
60–64	♂	1,073 (1,212)	1,749 (1,776)	2,591	3,347	3,687	3,719	3,561	3,349
	♀	186 (210)	235 (239)	295	342	432	527	678	833
65–69[c]	♂	1,031 (1,257)	1,798 (1,903)	2,964	3,965	4,879	5,304	5,215	4,986
	♀	222 (271)	315 (333)	369	396	532	673	819	992
70–74[c]	♂	799 (1,087)	1,442 (1,567)	2,678	3,924	5,020	6,252	6,899	6,694
	♀	251 (341)	337 (366)	408	470	560	748	900	1,082
75–79[d]	♂	685[e]	1,130[e]	2,087	3,345	4,530	5,931	7,425	8,033
	♀	238[e]	328[e]	436	494	582	741	923	1,117
80–84[d]	♂	—[f]	791[e]	1,444	2,271	3,423	4,578	6,160	7,554
	♀	—[f]	297[e]	402	461	565	661	905	1,008
85+[d]	♂	—[f]	497[e]	927	1,438	2,062	3,490	4,457	5,484
	♀	—[f]	201[e]	316	399	480	629	795	899

[a] Estimates corrected for undercertification (by the same factors as in the U.S. data; *see* table E2) appear in brackets after the data for 1941–45 and 1946–50. The more reliable figures are given in boldface type.

[b] To match the corresponding U.S. data in table E1, cancers of the nose and nasal sinuses start to be included after 1950, at which time they account for only 1% of respiratory cancer deaths.

[c] Moderately unreliable.

[d] Very unreliable, especially in early years.

[e] Correction not attempted for early years; true rates cannot be estimated directly.

[f] Published data not subdivided above 80.

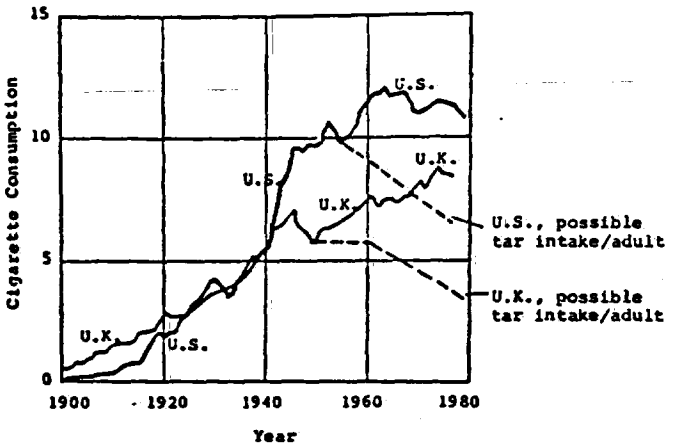
TABLE E1.—*Annual death certification rates/million people for all races in the United States, from cancer of the lung*[a] The more reliable figures are in boldfaced type.[b,c]

Age, yr	Sex	Annual death certification rates/million people, for: 1933–37 (≈1935)[b]	1938–42 (≈1940)[b]	1943–47 (≈1945)[b]	1948–52 (≈1950)[b]	1953–57 (≈1955)	1958–62 (≈1960)	1963–67 (≈1965)	1968–72 (≈1970)	1973–77 (≈1975)	1978 only
30–34	♂	12	15	17	17	19	24	24	21	18	17
	♀	8	8	8	8	8	8	10	11	10	11
35–39	♂	26	31	39	44	46	60	73	78	71	62
	♀	14	13	18	16	17	22	28	37	36	35
40–44	♂	56	73	94	107	128	151	183	219	206	192
	♀	25	27	29	29	34	46	64	87	102	108
45–49	♂	101	153	187	246	297	333	392	465	502	480
	♀	37	45	52	52	58	79	114	161	212	235
50–54	♂	159	243	353	467	578	669	767	871	949	1,021
	♀	56	68	81	81	84	109	164	269	333	408
55–59	♂	211	347	542	739	960	1,142	1,279	1,505	1,583	1,647
	♀	84	100	125	116	116	145	206	349	490	571
60–64	♂	237	408	641	969	1,320	1,665	1,975	2,247	2,486	2,625
	♀	105	131	159	164	159	184	247	389	617	767
0–64[d,e]	♂	47	73	105	143	183	219	254	293	314	325
	♀	19	23	27	27	27	34	47	73	100	118
65–69[c]	♂	244	417	630	1,052	1,582	2,064	2,571	3,110	3,390	3,557
	♀	124	164	194	218	220	231	294	460	671	876
70–74[c]	♂	235	378	588	1,032	1,551	2,113	2,740	3,551	4,186	4,522
	♀	148	179	239	286	279	282	332	483	691	871
75–79[c]	♂	233	370	530	928	1,355	1,804	2,572	3,453	4,358	4,760
	♀	139	187	255	364	361	344	372	498	683	864
80–84[c]	♂	170	295	421	770	1,148	1,523	2,046	2,913	3,814	4,580
	♀	113	166	215	357	391	394	411	537	646	802
85+[c]	♂	153	223	319	676	876	1,209	1,574	2,173	2,754	3,165
	♀	72	118	161	353	370	402	451	557	652	686
65+[c,d]	♂	224	369	552	963	1,428	1,902	2,482	3,202	3,792	4,136
	♀	128	169	218	290	294	298	344	490	675	850

[a] Estimated as "all respiratory sites except larynx."
[b] Rates in or before 1950 become progressively less reliable the farther back one goes, and are affected by minor errors of population undercount and by the exclusion of cancers of the nose, nasal sinuses, and other sites. (*See* tables E2 and E3 for corrected estimates.)
[c] Rates at ages >65 yr are progressively less reliable with increasing age.
[d] Standardized to the age distribution of respondents to the U.S. 1970 census (*see* appendix A).
[e] Standardization to ages 0–64 yr conceals the differences in direction between the recent trends above and below the age of 50 yr.

these decreases should continue through the 1980's (and during the 1980's should spread to the age groups 50–54 and 55–59, of course). Text-figure E3 presents the rates only from 1950 onward, for reasons which have already been discussed at length in appendixes B, C, and D, but some of these reasons probably apply with greater force to lung cancer[6] than to any other

[6] In 1900, most people dying of lung cancer would never have been diagnosed as having lung cancer, either while still alive or (since only a minority of people would have been examined post mortem) after having died of lung cancer. Over the subsequent 50 years the techniques for diagnosing lung cancer were enormously improved by the introduction of X-rays, bronchoscopy, intrathoracic surgery, and sputum cytology, by increasingly reliable distinction between primary and secondary cancer in the lung, and by the introduction of sulfa drugs and antibiotics which cured potentially fatal chest infections due to unrecognized cancers and so permitted those cancers to be recognized. Moreover, medical coverage of the population improved. In 1900 many lung cancer patients would never have been admitted to hospital, but by the middle of the century Americans of working age who developed lung cancer would typically be investigated in hospital, with postmortem examinations of many who died before a definitive diagnosis had been established. By 1950 most people dying in middle age of lung cancer would probably have been correctly diagnosed, either before or after death, and no great improvements in diagnostic technology for lung cancer have been introduced since then. This improved diagnosis may have been of little value for the patient (since ≈90% of all cases of lung cancer are still incurable when diagnosed), but it improved the accuracy of death certification, producing large artifactual upward trends in lung cancer death certification rates throughout the first half of this century. These artifactual trends were so large in the early period (Enstrom, 1979) that we shall present the data only from 1933, the year in which nationwide collection of causes of death in America began. Even between 1933 and 1950, however, some fairly large artifactual trends must also have occurred, chiefly upward. (As the correct diagnosis of lung cancer became less and less of a medical rarity between 1900 and 1933, an increasing tendency to misdiagnose other causes of death as "cancer of the lung" may have developed, accentuating the artifactual upward trends. Progressive elimination of such errors around the middle of the century may then have diluted slightly the real upward postwar trends. This slight dilution could, of course, be important only where the absolute rates are low and the real upward trends are not large, as, for example, among American females between 1940 and 1960.)



TEXT-FIGURE E4.—Mean daily sales of manufactured cigarettes per U.S. adult over 18 years of age contrasted with the corresponding mean per U.K. adult over 15 years of age (Surgeon General, 1980; Lee, 1976).

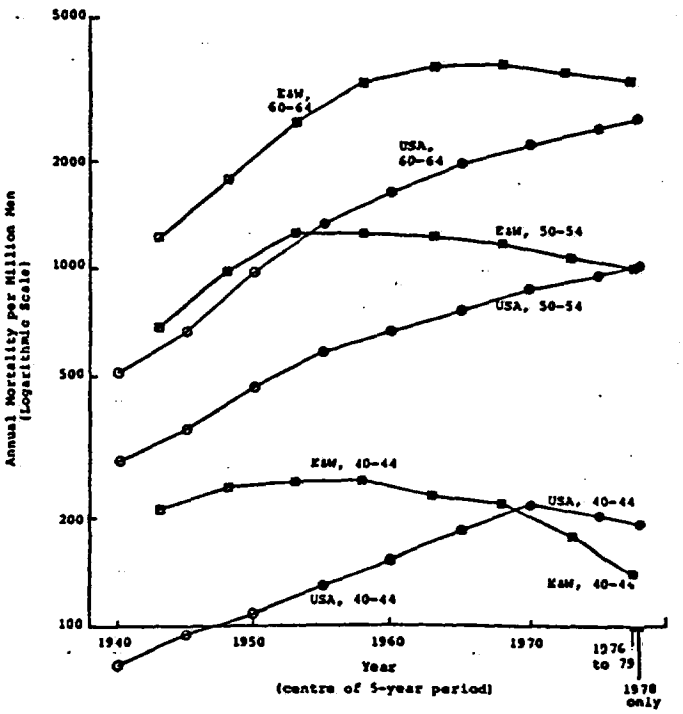
Since 1948 there have been annual surveys of British smoking habits (Lee, 1976), and although consumption per woman has risen steadily, consumption per male has remained constant. Broken lines provide a very crude and approximate estimate of tar intake per adult, expressed in "constant tar cigarettes" (Owen, 1976; Wald et al., 1981). British tar yields per cigarette were down 9% by the mid-1950's, down a further 14% by the mid-1960's, and down a further 27% by the mid-1970's; thus tar intake per British male has progressively decreased since 1948.

increases in female smoking), but tar yields per cigarette have been decreasing ever since World War II, so tar intake per young British man may have been roughly constant from the 1920's to 1950, with progressive decreases thereafter—a pattern very different from the sudden American midcentury peak in tar intake. Because of this, the "successive generation effect" (whereby differences between successive generations in smoking in early adult life imprint on those generations differences in predisposition to lung cancer in later life) may have roughly ended in Britain with the generation born early in this century. Consequently, the effects of the large decreases in tar yields per cigarette should be seen more easily in Britain than in the United States, for in Britain they are superimposed for many age groups on a gently rising or roughly constant (we cannot tell which) "successive generation effect"; whereas in the United States they are, initially at least, superimposed on, and therefore concealed by, the large "successive generation effect" increases due to the large mid-century peak in American tar intake, which Britain did not share.

British lung cancer.—The British lung cancer mortality data are conveniently available (Office of Population Censuses and Surveys, 1975) only from 1941 and are presented in table E4. (As with the American data, the British lung cancer data prior to 1950 become progressively less reliable; and the estimates in table E4, which are corrected approximately for under-certification, may be preferred for 1941–45 and 1946–50.) During the 1950's British male lung cancer death rates were decreasing only in the youngest age groups, during the 1960's these decreases had managed to spread throughout middle age (because they did not have to compete with a strong "successive generation effect"), and now they have spread to old age. Among British women, who (like American women) lagged about a quarter of a century behind men in their adoption of cigarettes, the "successive generation effect" is still strong in many age groups, and as yet only below the age of 50 can actual reductions in British female lung cancer rates be seen.

The British and American male mortality data for three particular age groups are contrasted in text-figure E5. Among British men born after the early years of the century, the "successive generation effect" should have moderated, and worthwhile decreases are indeed clearly evident, as should be expected from the postwar decreases in tar yields. (To display rates of 100/million and 5,000/million legibly on one graph, we have used a "log" scale in text-figure E5, on which an increase from 100 to 200 looks as large as an increase from 1,000 to 2,000. This log scale may misleadingly suggest that the decreases are not important, whereas in fact the decrease at ages 40–44 from 256/million to 146/million represents nearly a 50% risk reduction, and even the "slight" decrease at 50–54 represents silent prevention of one-sixth of the lung cancer deaths at these ages.)

The only odd feature of text-figure E5, in view of the similarity of the cigarette sales per adult in Britain and



TEXT-FIGURE E5.—Comparison of lung cancer trends in the U.S. (USA, *round symbols*) in selected age groups with corresponding trends in England and Wales (E&W, *square symbols*).

Data from tables E1–E4; points for 1940 to 1950 are estimates corrected for under-certification (open symbols); *points for subsequent years are observed rates* (solid symbols).

common type of cancer, and some self-explanatory corrected estimates for the male rates in the early years are suggested in tables E2 and E3. Readers who are unhappy with these particular corrections may devise alternative corrections, or they may ignore the data prior to 1950 as being wholly untrustworthy.[7] It would not, however, be advisable to infer from the trends in *uncorrected* lung cancer death *certification* rates before 1950 that any large upward trends in real lung cancer onset rates were taking place among American females or that the trends among males were as steep as the uncorrected data suggest. (Likewise, the trends since 1950 among very old Americans of either sex may be seriously in error.)

Examination of the top right-hand corner of table E1 shows that all the male lung cancer rates above the age of 50 have risen steadily from 1950 to 1978. Probably, however, for the reasons already discussed the rate among men aged 50–54 will reach a maximum by about 1980, the rate among men aged 60–64 will reach a maximum by about 1990 (or a little earlier, especially if tar yields continue to fall), and the rates for men in their 70's will reach a maximum by the turn of the century or earlier, after which male lung cancer rates as a whole should, other things being equal, be decreasing.

Female lung cancer data.—It is not surprising that nearly all the female rates in table E1 are still rising; indeed, it is slightly surprising, and rather encouraging, that the female rates at ages 30–39 seem to have stopped rising recently. A reasonable hope is that in view of the continuing decreases in tar yields, these particular female rates will not start to rise again. However, in view of the increase in female usage of cigarettes right up to the mid-1970's it is too soon to be certain. *If* this halt in the increase of lung cancer mortality for women in their thirties continues, then presumably it will gradually spread to older age groups of women. For example, since there has been no upward trend in lung cancer among women who were in their thirties during the 1970's, there should be no upward trend in lung cancer among these same women as they reach their fifties during the 1990's. This would suggest that by the turn of the century lung cancer rates among middle-aged women will no longer be rising. However, rates among older women will probably (depending on trends in tar yields and female cigarette usage in the intervening period) still be increasing due to the successive increases in tobacco exposure during early adult life of the successive generations of women born in 1920, 1930, and 1940.

Comparison of British and American Trends

Well over 90% of lung cancer deaths occur over the age of 50 where uniform upward trends in U.S. lung cancer mortality have been observed for decades. Yet, our interpretation of current trends in lung cancer mortality and our predictions of future lung cancer mortality depend chiefly on the small decreases that have been observed in recent years in the death rates among men aged under 50. This situation looks a bit like the "tail wagging the dog," and although we intended to avoid theoretical models, there is obviously a sense in which any predictions for 1980–2000+ are theoretical. However, the pattern of rapid increases in all age groups of men for a few decades, followed by gentle decreases first among men in early middle age, then among men in later middle age, and finally by older men, that we have predicted is not only what might theoretically be expected but also, more importantly, what has actually been observed in Britain and Finland, two countries where cigarettes have been used for many decades. It is therefore of interest to compare the American experience to date with the British and Finnish experience.

Cigarette usage by young British men.—Cigarette usage per adult in Britain and the United States is compared in text-figure E4. As has already been noted, the low usage per adult in the early period does not necessarily indicate a correspondingly low intake per young man. In both countries, to estimate the general shape of a graph of cigarette usage per young man in the early period, it *might* be reasonable to take the shapes of the graphs of U.S. and U.K. smoking before 1950 that are suggested by text-figure E4 and roughly double the figures for 1900–20. (World War I, which ended in 1918, would, of course, accentuate the difference in attitudes, values, *and habits* between young and old.) This procedure would suggest that during the 1920's and 1930's the cigarette smoking habits of young men in both countries either increased by a small amount or were approximately constant and that the increase in cigarette usage per adult between the wars was due chiefly to the spread of the habit to middle-aged and older men, and to women. Detailed data for the smoking habits of young men during 1900–40 do not exist in either country,[8] and we justify our rough suggestions partly by their intrinsic plausibility and partly by the unpleasantly circular argument that they do predict something like the observed lung cancer trends.

In Britain, cigarette usage per man has been constant since 1950 (the increases in text-figure E4 being due to

[7] Our view is that absolute mortality trends in the early years are difficult to estimate directly, but that trends in the ratio of male-to-female death certification rates at some particular age (e.g., 50–54) are not plausibly accounted for by artifacts of diagnosis, certification, or population estimation and are, therefore, informative. For further discussion of the biases and trends in the pre-1950 lung cancer data, *see* Dorn (1954).

[8] Detailed estimates of the exact age-specific cigarette usage by British men have been suggested by the Tobacco Research Council and appear in various of their publications (e.g., Lee, 1976), but these estimates are based on the unsupported assumption that the age distribution of cigarette usage did not change between the 1890's and the 1940's. This assumption does not appear to us to be plausible.

TABLE E5.—*Decreases in lung cancer, comparing 1978 data with data for the worst-affected[a] generations of men in England and Wales and in the United States*

Age, yr	England and Wales				United States			
	Worst-affected[a] generation (born ca. 1910–11)		Rates for 1978 compared with those for worst-affected generation		Worst-affected[a] generation (born ca. 1927–28)		Rates for 1978 compared with those for worst-affected generation	
	Mortality/ million men	Period of observation	Mortality/ million men in 1978	Decrease[b]	Mortality/ million men	Period of observation	Mortality/ million men in 1978	Decrease[b]
30–34	40	1941–45	17	58%/35 yr	24	1958–62	17	30%/18 yr
35–39	98	1946–50	63	36%/30 yr	73	1963–67	62	15%/13 yr
40–44	253	1951–55	138	45%/25 yr	219	1968–72	192	12%/8 yr
45–49	597	1956–60	385	36%/20 yr	502	1973–77	480	4%/3 yr
50–54	1,234[c]	1961–65	1,047	15%/15 yr	?	1980	1,021	—[e]
55–59	2,219[d]	1966–70	1,912	14%/10 yr	?	1985	1,647	—[f]
60–64	3,577[d]	1971–75	3,315	7%/5 yr	?	1990	2,625	—[g]
65–69	5,018[d]	1978	5,018	—	?	1995	3,557	—[g]

[a] These are the generations with the highest death rates at ages 35–44, when substantial effects of smoking first became evident. However, if in the future the number of cigarettes smoked/individual will decrease, or the effective dose of noxious chemicals/cigarette will decrease, the benefits at some particular attained age to these two worst-affected generations may be greater than to the immediately previous generations. The maximum American lung cancer rates in old age may therefore be seen, at around the turn of the century, in the generation born in a few years before this "worst-affected" generation.

[b] Percentage decrease, comparing age-specific mortality in 1978 with that for the worst-affected generation (born 1910–11 in England and Wales, born 1927–28 in United States).

[c] Might have been materially larger but for changes in cigarette composition.

[d] Would have been materially larger but for changes in cigarette composition.

[e] U.S. mortality at ages 50–54 should reach a maximum by ~1980.

[f] U.S. mortality at ages 55–59 is still rising.

[g] U.S. mortality at ages 60–64 and 65–69 is still rising rapidly.

"current" lung cancer rates are an (age-standardized) average of the lung cancer rates among several different generations of people, each with very different degrees of exposure to cigarette smoke in *early* adult life. If, however, attention is restricted to people of a given age (e.g., 35–44) whose adult lives have been passed under the reasonably stable social conditions that have on the whole prevailed since the end of World War II (and after the end of the immediate postwar austerity period in Europe), there is a reasonable correlation between national cigarette consumption rates per adult when those people were young and their lung cancer risks as they enter middle age (text-fig. E6). This correlation is rather better than we would have expected in view of the possible international differences in cigarette composition, puff frequency, style of inhalation, butt length, additional use of non-manufactured cigarettes (and other forms of tobacco), and national consumption of cigarettes in the intervening years between 1950 and 1975.[11] However, even if the apparent closeness of the correlation in text-figure E6 is partly due to chance, it does emphasize that the "poor" international correlations that are sometimes used as arguments against the overwhelming importance of tobacco may be "poor" chiefly because they were effectively seeking a correlation between the smoking habits of one generation and the lung cancer risks of their parents or grandparents.

TABLE E6.—*Annual lung cancer incidence/million men, Finland*[a]

Age, yr	Annual incidence/million men, for:	
	1967–71	1972–76
30–34	8[b]	11[c]
35–39	56	43
40–44	207	186
45–49	630	518
50–54	1,369	1,340
55–59	2,783	2,514
60–64	4,332	3,923

[a] Average of the 5 most recent available incidence rates (1972–76) and the 5 previous incidence rates (1967–71).

[b] Based on only 6 cases.

[c] Based on only 9 cases.

Recapitulation

Current increases in male U.S. lung cancer mortality are following the qualitative pattern that one should expect from the large mid-century peak in cigarette tar intake per U.S. male. Because of this mid-century peak, there have been during recent decades large lung cancer increases due to the "successive generation effect" having imprinted successively increasing predisposi-

[11] The effects of the imperfect correlation between the smoking habits of all adults and of young adults in 1950 may be somewhat offset by the presumably opposite effects of this correlation in the intervening years.

the United States during 1925–40 (text-fig. E4), is that the American death rates for men born in about 1910 are only half the corresponding British rates. It seems probable, however, that the tar intake per young British man between the wars considerably exceeded that per young American man (because of differences in tar intake per cigarette,[9] and possibly also because of differences in the number of cigarettes smoked per young man[10]), and this phenomenon may be the whole explanation for the previous excess British risk. Since 1945, American cigarette usage suddenly began greatly to exceed that in Britain (and the spending power of American youths increased rapidly). Presumably as a result of this, among men aged 40–44 there has been a crossover in about 1970 between British and American lung cancer mortality (text-fig. E5) which is likely to be repeated in about 1980 at ages 50–54 and in about 1990 at ages 60–64. The British data are of interest because, especially in the youngest age groups, they may provide a better indication of the benefits to be expected from changes in cigarette composition, for these benefits are not as completely swamped as they are in most of the American data by the "successive generation effect." Table E5 documents the magnitudes of the risk reductions that have already been observed in England and the United States. Of course, there is no guarantee that cigarette usage has been exactly constant among young adults over the relevant periods, so the true benefits from changes in cigarette composition may be a little less or, more probably, a little more, than is suggested by the comparisons in table E5. However, this table strongly suggests that substantial benefits have already accrued, and it seems reasonable to expect further substantial decreases during the next decade or two.

Comparison With Finnish Data

Among countries with good data on recent lung cancer and on cigarette usage (Lee, 1975) half a century ago, the only country outside the British Isles and North America where people already smoked substantial numbers of cigarettes between the two World Wars is Finland. In Finland, average cigarette consumption between 1920 and 1940 was 3.7/adult/day, which was then very similar to that in Britain and the United States (text-fig. E4), but Finland, like Britain, did not have the large increase in cigarette usage between 1940 and 1945 that was seen in the United States. Consequently, Finnish lung cancer rates throughout middle age have, like the British rates, already stabilized and begun to fall (table E6).

Table E6 presents lung cancer incidence data and therefore includes both fatal and non-fatal cases. However, if the Finnish rates in the late 1960's are multiplied by about 0.9 to "remove" the non-fatal cases, we get rates in middle age very similar to the corresponding British rates and much higher than the corresponding U.S. rates. Air pollution in rural Finland is negligible (except perhaps in sauna baths!), and even the Finnish cities have never been highly polluted in comparison with British standards. In section 5.7 we did not ascribe any large fraction of lung cancer to air pollution, either acting alone or synergistically with cigarettes. Comparison of the British and Finnish data confirms that *a*) there is no need to assume any large effects of air pollution to get the high levels of lung cancer per cigarette observed in Britain, and that *b*) there is no need to invoke decreases in air pollution to explain the recent decreases in British and American lung cancer mortality.

Other Countries

There are, of course, many countries other than the United States, Britain, and Finland where the relationship between cigarette smoking and lung cancer could have been examined. Although each has its special peculiarities, we know of no country where causes of death are reasonably accurately certified yet the certified lung cancer death rates in middle age are grossly discrepant with what is known of the smoking habits in that country in previous decades. The greatest apparent discrepancy at present is perhaps Japan, where there is less lung cancer than might have been predicted; however, the current rate of increase of Japanese lung cancer death certification rates is so rapid (*see* table 5 on page 1202) that during the 1980's this anomaly may disappear. Because of the strong influence of cigarette consumption in early adult life on lung cancer risks in later life (text-fig. E1), a close correlation between *current* cigarette consumption and *current* lung cancer rates should not exist, especially if

[9] In the 1950's, before the advent of filter tips, Americans habitually left much longer "stubs" unburned when they finished each cigarette than did British men (Doll et al., 1959: differences in stub length between American and non-American cigarettes were also obvious to one of us who, in his early teens, habitually scavenged the roads around Southampton docks for smokeable stubs discarded by sailors of various nations). The tar yield from the last few puffs from a short hot stub exceeds that from the first few puffs from a cigarette. In recent decades, however, the advent of filter tips has prevented British men from smoking their cigarettes down to tiny stubs.

[10] *a*) The ratio of young men to adults between the wars was larger in the United States than in Britain, and young men were the principal consumers of cigarettes. The ratio of the number of cigarettes sold to the number of young men would be larger for Britain than for the United States.

b) World War I lasted longer and killed far more young men in Britain than in the United States and so may have produced a larger divergence in attitudes and habits between young and old in Britain. (Although the Vietnam War killed only 1% as large a proportion of young American men as the 1914–18 war killed of British men, it too produced a divergence of attitudes and drug use between young and old.)

c) Any slight differences in average age at starting to smoke substantial numbers of cigarettes regularly could have a large effect on subsequent risks, but there is no evidence bearing on British or American practice on this in earlier decades.

Comparison With Other Interpretations of Trends in U.S. Lung Cancer

The interpretation that we have offered of the U.S. lung cancer trends differs sharply from that put forward by the Council on Environmental Quality in the 1980 inter-agency report to the President of the United States by the Toxic Substances Strategy Committee (entitled "Toxic Chemicals and Public Protection"). The TSSC report, which closely followed an unpublished analysis by Schneiderman (1979), obtained considerable publicity when it was released, both in the lay and scientific press [e.g., the long report in the influential journal *Science* (*209*:998–1002) entitled "Government says cancer rate is increasing"]. The TSSC concluded that large increases in lung cancer were occurring over and above those attributable to smoking, but their analysis was based on the absurd assumption that if American smoking habits (and any other relevant exposures) had been constant from the 1960's to the 1970's there would have been no large trends in lung cancer over this period! This extraordinary failure to expect any large increases due to the "successive generation effect" is a simple scientific error to be corrected, rather than a new scientific hypothesis to be considered, because massive "successive generation effects" have been seen or are being seen in every country that has adopted cigarette smoking on a large scale before the middle of this century. If *new* (e.g., since 1950) toxic chemicals or occupational carcinogens were now having any really substantial effects on U.S. lung cancer trends, then their percentage effect would be expected to be largest among men in their 30's, 40's, and perhaps 50's rather than among men in their 60's and 70's, whereas in fact we observe rapid increases among men in their 70's and *de*creases among men under 50.

Any analysis is bound to be misleading if, as the TSSC did in its Council on Environmental Quality report, it averages together (by age standardization) the upward trends in old age due to the pre-1945 increases in cigarette usage by young adults and the downward trends in early middle age where the pre-1945 increases have had their full effect and so have ceased to dominate the trends. The essence of any reliable interpretation of trends in cancer incidence is separate examination of the trends among each separate age group, as was already being undertaken for U.S. lung cancer mortality more than a quarter of a century ago by Dorn (1954), with conclusions rather similar to our own. Only if no important differences in (at least the directions of) these separate trends is evident should they be averaged together by "age standardization," and even then it is wise not to combine the data for people over 65 with that for people under 65.

Failure to comply with this basic principle of cancer epidemiology (together with various other serious errors of judgment in matters of epidemiology[12] has led the Toxic Substances Strategy Committee to suggest that a large group of cancers are increasing extremely rapidly due to presumably occupational factors. Had they examined, in a standard way, trends in *mortality* data in middle age or among people aged 35–44 (*see* appendix D), no such conclusion would have emerged.

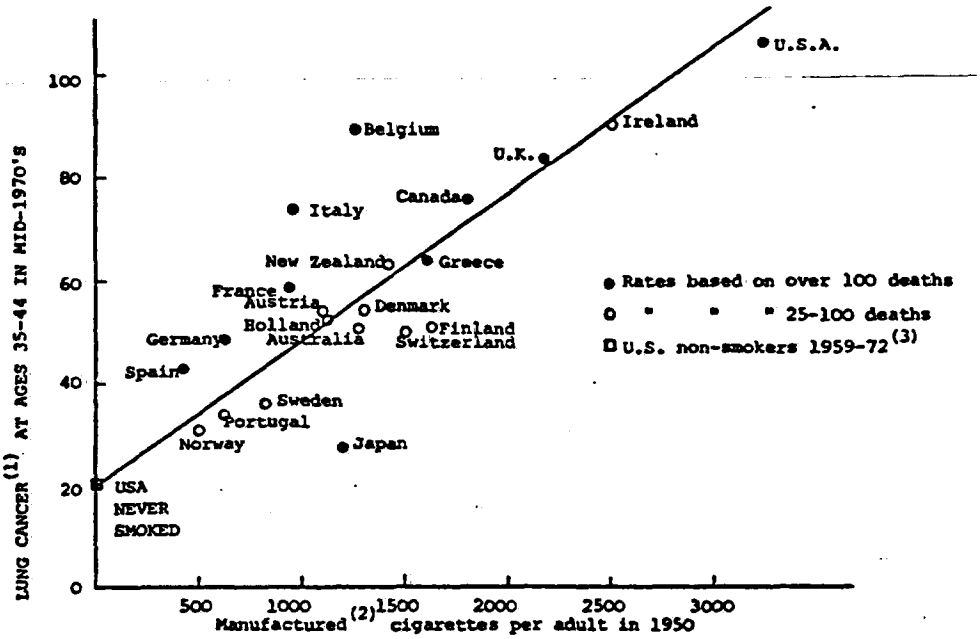
However, this very fact emphasizes the weakness of any analysis of national trends as a means for detecting the effects of causes of cancer like asbestos which, though important, probably only increase the incidence of some common type of cancer by a few percent (*see* section 5.6). We have scrutinized the U.S. lung cancer trends spanning the postwar period, during which period occupational exposure to asbestos has increased substantially, probably by now causing some thousands of lung cancer deaths a year. However (like the avoidance of some risk in the older age groups due to lowered tar yields), this is not clearly evident from the trends alone. Moreover, it might not have been unequivocally evident even if the large increases due to cigarettes had roughly stabilized long ago. Clearly, the effects of some other cause of cancer as important as asbestos could also lie unnoticed in these trends, especially if, like asbestos, its effect is to multiply up the effects of tobacco.

We have shown that the most important parts of the pattern of trends in age-specific lung cancer death certification rates *can* be explained by plausible assumptions about the effects of smoking, but this does not mean that those plausible assumptions are exactly true. Thus we do not claim to have shown that no important causes lie buried in the lung cancer trends, but merely to have shown that the trends themselves do not provide any strong evidence for the existence of any such causes. Despite this reservation, however, the downward lung cancer trends among males in early adult life remain moderately reassuring.

Trends In Lung Cancer Among U.S. Non-Smokers

This conclusion might in principle be tested in another way by examination of the trend in non-smokers. Enstrom (1979a) has shown that, from 1900 to the present, lung cancer death *certification* rates among non-smokers have risen, the largest relative increase being between 1900 and 1950, which he (and we) dismiss as being largely or wholly an artifact of death certification practice, with both "largely" and "wholly" being possible, and little chance of rendering either implausible. Since 1950 there have also been artifactual

[12] The most important other error (apart from implicitly assuming that no "successive generation effects" should exist) was to use, instead of mortality data, the trends in incidence suggested by comparison of the 1969–71 TNCS incidence data with the 1973–76 SEER incidence data. (*See* appendix C for criticism of this procedure.) Lesser errors include the use of "all-ages" rates instead of "under 65" rates (or, preferably, age-specific rates for some middle-aged age groups) and the construction of a category of cancers that were supposed to be those "most likely" to be related to occupational factors, but that included tumor types, such as kidney, melanoma, and myeloma, for which there is little independent evidence to suggest any unusually close relation to occupational factors.



TEXT-FIGURE E6.—International correlation between manufactured cigarette consumption per adult in 1950 while one particular generation was entering adult life (in 1950) and lung cancer rates in that generation as it enters middle age (in the mid-1970's).
Comparison has been restricted to developed countries (i.e., excluding Africa, all of Asia except Japan, and all except North America) with populations >1 million, to improve the accuracy of the observed death certification rates as indicators of the underlying risks of lung cancer among people aged 35–44.

(1) Lung cancer death certification rates per million adults aged 35–44 are from WHO (1977, 1980). These rates are the means of the male and female rates for all years (1973, 1974, or 1975) reported in WHO (1977), except for Greece [which was not reported in WHO (1977) and thus was taken from WHO (1980)] and Norway, for which the rates in WHO (1977) and WHO (1980) were based on only 11 and 14 cases, respectively; for statistical stability, these were averaged.

(2) Manufactured cigarettes per adult are from Lee (1975) for the year 1950 (except for Italy, where consumption data are available in 5-yr groups only; to avoid the temporary postwar shortages, data for 1951–55 have been used). This excludes handrolled cigarettes, which in most countries accounted for only a small fraction of all cigarette tobacco in 1950.

(3) U.S. non-smoker rates were estimated by fitting straight lines (on a double logarithmic scale) to the relationships between lung cancer mortality and age reported for male and for female lifelong non-smokers by Garfinkel (1980) and averaging the predicted values at age 40. [Although the average of the male and female rates actually observed at these ages is similar to this estimated value, these observed rates are each based on fewer than 5 cases (Garfinkel, 1980) and so might have been inaccurate.]

tions to subsequent lung cancer on the successive generations of American men born up to 1930. These increases in lung cancer mortality will probably continue at least up to the turn of the century among older American males.

Quantitatively, the American increases are not quite as large as comparison with Britain and Finland would have led one to expect, possibly because of some relatively less noxious aspect of American cigarette composition and probably because Americans took fewer puffs from each cigarette or in some other way exposed the key target areas in the lungs to less chemical damage per cigarette.

Worthwhile decreases, probably due to the switch to less hazardous cigarettes, are evident in those U.S. age groups (born since 1930) in which the rapid increases due to the "successive generation effect" have abated. Although worthwhile risk reductions may also have been conferred on older age groups by the switch to less hazardous cigarettes, these are not sufficient to override the rapid upward trends still occurring in older age groups due to the "successive generation effect."

In lung cancer, as for most other types of cancer, the key piece of evidence that should be examined to determine the net effects on adults of any new factors that have recently begun to operate is the trend among the *youngest* age groups (e.g., 35–44) in which any material effects of the causative agent could be expected (*see* table D6 on page 1287). If the trend in these *youngest* age groups is downward, as for stomach cancer, female genital cancer, male lung cancer, and pancreatic cancer, any recent net changes are likely to have been for the better, and the effects of these changes will probably spread to older age groups in the future. If the trend in these *youngest* age groups is upward (as for melanoma among males), then the opposite is true. The trends in the older age groups (e.g., 65–74) may chiefly reflect, via the "successive generation effect," the delayed effects of changes in exposure that occurred many decades ago. Consequently, in the trends among older people, the effects of even quite large recent changes in exposure may be difficult to discern (even though complete cessation of smoking leads to very substantial avoidance of risk within less than a decade).

TABLE E7.—*Lack of apparent upward trend in cancer of the lung, and in other smoking-related types of cancer, among male U.S. non-smokers*[a,b]

Type of cancer	Years since entry to study						
	1	2, 3, 4	5, 6, 7	8, 9, 10	11, 12, 13	14, 15, 16	All study years
Lung, observed	6	24	31	40	41	35	177
Lung, expected[c]	6.5	23.6	30.9	39.2	43.9	33.0	177.0
Ratio:observed/expected	0.9	1.0	1.0	1.0	0.9	1.1	1
Other smoking-related cancers							
MEPL,[d] observed	4	9	9	11	10	6	49
MEPL,[d] expected	2.3	7.4	8.9	10.3	11.6	8.6	49.0
Bladder, observed	9	16	22	17	31	29	124
Bladder, expected	4.0	12.3	16.9	24.4	33.6	32.9	124.0
Pancreas, observed	8	30	42	31	50	34	195
Pancreas, expected	7.9	28.7	36.4	40.5	43.6	37.9	195.0
Total,[e] all above smoking-related cancers							
Total, observed	27	79	104	99	132	104	545
Total, expected	20.6	72.0	93.2	114.3	132.6	112.4	545.0
Ratio:observed/expected	1.3	1.1	1.1	0.9	1.0	0.9	1

[a] Mortality among the 2 samples of male U.S. veterans who, in early 1954 (sample 1) or early 1957 (sample 2), had "never smoked regularly," monitored from mid-1954/57 to mid-1970.

[b] We are greatly indebted to Dr. Eugene Rogot, of the National Heart, Lung, and Blood Institute, who devised and performed these analyses and provided us with the results of them.

[c] Numbers of deaths observed are compared with the (indirectly standardized) numbers expected if, among men of a given single year of age in a given sample, death rates were unrelated to calendar year.

[d] MEPL denotes mouth, esophagus, pharynx, and larynx.

[e] Total of all the above smoking-related cancers (lung, mouth, esophagus, pharynx, larynx, bladder, and pancreas).

relation to smoking habits and occupational factors which we have recommended (in sections 5.1, 5.6, and elsewhere) will be *a*) to provide a direct estimate of the effects on non-smokers of passive smoking by their parents or spouses, and *b*) to provide a direct estimate of the absolute lung cancer death rate among non-smokers, for comparison with the past rates recorded in the above two studies and with any future estimates that may become available later this century.

APPENDIX F: EXAMINATION OF THE ARGUMENTS AND CONCLUSIONS IN "ESTIMATES OF THE FRACTION OF CANCER IN THE UNITED STATES RELATED TO OCCUPATIONAL FACTORS" (OSHA, SEPT. 15, 1978)

In the main text (pages 1240–1241), we stated our opinion that the estimates made in the OSHA document could not be regarded as having any validity, primarily because the implicit assumption was made that the industrial conditions that had been recognized as giving rise to gross hazards of occupational cancer were typical of the conditions to which 11.9 million workers in the United States were currently exposed. We examine here in detail the reasons for our conclusion.

For example, a total of 7,300 excess respiratory cancers (other than nasal sinus cancer) was "projected" (OSHA, 1978) to occur each year in workers exposed to nickel as follows:

> A Norwegian study of Pedersen et al. in 1973 observed an overall excess respiratory cancer incidence of 5.6-fold among nearly 2,000 men exposed to nickel. The highest risk (risk ratio of 14.0) was observed in men first employed before 1930 and followed for at least 40 years. Assessing that an overall risk ratio of about 5 for all respiratory cancers can be applied to the approximately 1,400,000 [U.S.] workers estimated to be exposed to nickel [in 1972], it is projected that about 7,300 excess respiratory cancers, excluding nasal cancer, will occur each year.

Arithmetically, this calculation is correct: The age-adjusted annual risk of lung cancer among males more than 20 years old in the United States was 0.00131, so a fivefold risk ratio would correspond to an excess annual risk of (5-1) × 0.00131, or 0.00524, the multiplication of which by 1.4 million does indeed yield a figure of 7,300. This calculation, however, might fairly be described as a confidence trick. It takes an estimate of risk from Norway and assumes that the same *relative* risk of respiratory cancer would apply to the United States where the normal incidence of the disease was much higher. It further assumes that the 1,400,000 workers currently "exposed to nickel" in the United States have been exposed to the same amounts as men employed in a nickel refinery, most of whom began employment under very dusty conditions [as is made clear in the publication by Pedersen et al. (1973)], despite the fact that many less than 1% of all American nickel workers are employed in refineries, that no hazard from exposure to nickel has been demonstrated outside a refinery, and that it is uncertain which specific nickel compound is carcinogenic to humans (IARC Working Group, 1980). This projected number

increases in lung cancer death certification rates in old age, but the question that we want to address now is whether since 1950 there has been any material upward trend in the *real* lung cancer death rate among middle-aged non-smokers.[13]

Enstrom (1979a) tried to answer this question in two ways, but both may be seriously biased by confusion of ex-smokers with lifelong non-smokers. In his first method, the numbers of non-smokers in a sample of the U.S. population were estimated directly by questioning the people concerned, so those who described themselves as lifelong non-smokers presumably were. In contrast, to estimate the annual numbers of deaths among lifelong non-smokers, he used data from the national mortality surveys of 1958/59 and 1966/68, in which the smoking habits of some thousands of people who had died of lung cancer were estimated by writing to the "informant" listed on the death certificate (i.e., the person who had informed the U.S. Government of the fact of death) asking various questions about the dead person, one question being whether the dead person had smoked. This method inevitably leads to misclassification of some ex-smokers as being "lifelong non-smokers," and so inevitably leads to an overestimation of the number of lung cancer deaths among "lifelong non-smokers." The magnitude of this overestimation will presumably increase as the lung cancer epidemic increases among smokers. Some estimate of its magnitude in the mid-1960's may be obtained by comparing lung cancer death rates in the American Cancer Society's prospective study of *self*-described non-smokers (Garfinkel, 1980) during 1960–72 with the rates estimated as above from the 1966/68 national mortality survey. Standardized for age,[14] the annual male death rate was 14±1 per 100,000 *self*-described non-smokers versus 25 per 100,000 estimated as described above. This difference suggests that *a*) the percentage of lung cancer patients who have never smoked may be substantially smaller than is suggested by the national mortality surveys, and *b*) trends in lung cancer mortality suggested by comparison of these surveys cannot be trusted, especially since the proportion of relatively recent ex-smokers may have altered substantially over the past quarter century, and since the question asked of the informants in the two surveys defined "non-smokers" differently.

Enstrom's (1979a) second argument involves the lung cancer death rates observed during the first few years of the two largest American prospective studies of mortality among people who at the beginning of those studies (in the 1950's) said that they had never smoked regularly. These non-smoker lung cancer death rates, relating to about 1960, are then compared with the lung cancer death rates estimated (with some methodological difficulties) during 1968–75 among active Mormons, almost none of whom are current smokers. However, about one-third of active Mormons in California are ex-smokers (Enstrom, 1975, 1978), so although the lung cancer death rates of active Mormons in California and Utah in about 1972 were estimated to be about double those of the self-described *lifelong* non-smokers in about 1960, this is not evidence that non-smoker death rates increased at all between 1960 and the early 1970's.

A more natural comparison would be of the lung cancer death rates among the self-described non-smokers in the early years of these two prospective studies of self-described non-smokers with their death rates in the later years of those same studies, preferably excluding (or examining separately) the first year or two after recruitment because there may well be a shortage of lung cancer deaths in the first year if people who already have lung cancer are not enrolled.

First, in the ACS study, Hammond (1977) determined the smoking habits of one million men and women in 1959 and monitored all causes of death among most of them until mid-1972. Some of the men and many of the women claimed that they had never smoked regularly, and 189 male and 503 female lung cancer deaths accumulated during 1960–1972 among these 1,959 non-smokers (Garfinkel, 1980), but no material trend in lung cancer mortality among middle-aged non-smokers of either sex was evident (Garfinkel L: Personal communication; *see* also Garfinkel L, 1981), a conclusion likely to be strengthened rather than weakened if the first year after recruitment (mid-1960 to mid-1961) were excluded.

Second, Dorn determined the smoking habits of more than a quarter of a million U.S. veterans in 1954 or 1957, and any deaths among them before mid-1970 have been traced (Rogot and Murray, 1980). Detailed data for the non-smokers among these veterans have been made available to us by E. Rogot of the National Heart, Lung, and Blood Institute, and again no evidence of any upward trend in lung cancer among non-smokers is apparent (table E7). Pending further data, we remain unconvinced that any material trends in true lung cancer death rates among American non-smokers have occurred in recent decades (although some such increases should be expected if the effects of "passive" smoking reported by Hirayama (1981) and Trichopoulos et al. (1981) are confirmed). A fortiori, we are even less convinced that any such trends not attributable to passive smoking among non-smokers have occurred. We note that two incidental by-products of the large case-control study of lung cancer in

[13] One might expect such a trend merely from the effects of "passive" smoking on non-smokers (Hirayama, 1981; Trichopoulos et al., 1981), although *a*) the use of pipes and cigars which preceded use of cigarettes must have created some effects of passive smoking early this century, and *b*) any effect might take about 20 yr longer than the effects on smokers to show up, since presumably if any material effect of passive smoking really exists then heavy exposure in childhood will ultimately lead to the greatest risk. Also, to judge by the sales of manufactured cigarettes (text-fig. E1), children have been really heavily exposed only since 1945.

[14] Standardized in 10-yr age groups to the population of respondents aged 35–84 to the 1970 U.S. census, taking death rates at ages 75 and over to apply to 75–84.

or gastrointestinal cancer is indicated by Selikoff's studies of various groups of insulation workers and adds up "to a total of 35–44%," as against a proportion of 8–9% who would have been expected to die of cancer of these sites in the absence of exposure to asbestos; and *b*) that a further 4–7 million workers who have been less heavily exposed experience an excess risk of "one-quarter of that to the heavily exposed workers." It is then deduced from the first assumption that "at least 1.6 million" of the heavily exposed workers "are thus expected to die of the asbestos-related cancers listed above" and from the two assumptions (OSHA, 1978) combined that

> . . . the total number of cancers attributable to asbestos in the less heavily exposed group would be expected to be in the range of 0.4 to 0.7 million, raising the total to 2.0 to 2.3 million. Since most of these cancers will be manifested over a period of 30–35 years, the expected average number of cancer deaths associated with asbestos per year in that period will be between 58,000 to 75,000. Such numbers would comprise 13–18% of all cancer deaths expected in the United States in the for[e]seeable future (assuming that total cancer deaths increase to 400,000 to 450,000 per year).

Their argument is impossible to follow in detail, because of the inconsistencies in the allowance that is made for the normal background incidence of cancers of the lung and gastrointestinal tract,[2] the terms "asbestos related," "attributable to asbestos," and "associated with asbestos" being inappropriately interchanged in places. Rectification of these inconsistencies would, however, alter the predictions of the total effects of asbestos by only about one-fifth, which is relatively unimportant. The more important question is whether the large estimates of risk, which the OSHA paper carries over from Selikoff's studies of people who have been occupationally exposed as shipyard insulation workers for decades, really are applicable to about 10% of the men in the whole United States[3] (half of whom are less than 40 years of age). We have no means of testing this directly, but the internal evidence of Selikoff's own studies makes it extremely unlikely. We note, for example, that the estimate of 8–11 million American workers who had been exposed to asbestos in the United States since the beginning of World War II included 4.5 million who had worked in shipyards during the 1940's and that this work force was extremely mobile with a labor turnover each year that averaged more than 100/100 employees between 1941 and 1945 (Selikoff et al., 1979). The average duration of exposure per man in such a transient work force would, of course, be fairly brief, and of course while they were employed not all of them would be heavily involved with asbestos insulation. In contrast to this, the men that had been studied by Selikoff (42% of the recent deaths among whom were attributed to asbestos-related cancers) were men employed as shipyard insulation workers in 1967 and whose first employment as such had been 20 years or more previously (Selikoff et al., 1979). These were, therefore, for the most part long-term employees with a prolonged and specific exposure to the hazards of insulation, quite different from short-term employees in other shipyard trades.

Another check on the validity of the estimates can be obtained by comparing the estimated numbers of mesothelioma deaths with the numbers that actually occur. Since the authors' figures require 7–10% of heavily exposed workers to die of pleural or peritoneal mesothelioma, it follows from their argument that there should be between 350,000 and 575,000 deaths from asbestos-related mesothelioma over the postulated period of 30–35 years (7–10% of 4 million and one-quarter of 7–10% of 4–7 million; here, the authors' arithmetic inconsistencies in allowing for normal background have a negligible effect, because the spontaneous incidence of mesotheliomas is so small). The claim that these calculations refer mainly to future effects and that "an estimate of the present-day numbers of cancers attributable to asbestos would undoubtedly be smaller" does not make much sense, as the large proportion of asbestos-exposed workers whose exposure was in the shipyards during the war (41–56% of the total) must already be suffering near peak absolute rates, if indeed their peak is not already past due to the normal attenuation of the number at risk through death in old age and the specific attenuation of cigarette smokers due to the multiplicative effect of exposure to the two agents.

If, therefore, the OSHA calculations are correct, and 350,000–575,000 mesotheliomas will really occur over 30–35 years, at least 10,000 per year should be occurring already, and they are not.

Cancer registry data suggest that approximately 900 cases were diagnosed each year in the early 1970's (Hinds, 1978), giving an annual incidence of approximately 7 per million in men and 2 per million in women. A detailed study of 188 cases diagnosed in Los Angeles county between 1972 and 1979, where the incidence in each sex was close to the estimated national rate, suggests that about 70–80% of the male patients and 10–20% of the female patients had been specifically exposed to asbestos (Henderson and Peto,

[2] There appear to be two inconsistencies. *a*) If, as is assumed, 35–44% of heavily exposed men and 8–9% of unexposed men get certain types of cancer, and if, as is assumed, the excess risk among the less heavily exposed is one-quarter that among the more heavily exposed, then it should be 7–9%, not 10%, among the 4–7 million less heavily exposed. *b*) It is not stated in unequivocal terminology exactly what the figures 2.0 to 2.3 million are supposed to be. If, as the context in subsequent pages makes probable, they refer to the number of deaths that could have been prevented by avoidance of asbestos, then it was an oversight not to have subtracted the 0.35 million background cancers expected anyway among the heavily exposed workers.

[3] OSHA (1978) estimated that approximately 1 million of the 8–11 million American workers who had been exposed to asbestos in the United States since the beginning of World War II had already died, leaving 7–10 million (most of whom would have been male) still alive, which amounts to about 10% of the 1978 U.S. adult male population of 73 million (table B1).

of incident cases is then approximately doubled,[1] to yield an estimate of about 15,000 lung cancer deaths per year over the next few decades due to exposure to nickel in or before 1972–74.

The impropriety of the whole calculation is underlined by the fact that the risk of respiratory cancer that used to be observed in nickel refineries included a risk of nasal sinus cancer that caused about a third as many excess deaths being certified as due to cancer of this type as were certified as being due to cancer of the lung, so that the above 15,000 lung cancers suggest that nickel should be responsible over the next few decades for about 5,000 nasal sinus cancer death certificates a year (unless, with the increase in national lung cancer death rates, the ratio of nasal sinus to lung cancer among nickel refiners has greatly decreased). Nickel has been widely used for decades, so if such a total is ever to be attained we should already be a fair way toward it. In fact, in the entire United States during 1973–77 there were on the average only 274 male deaths each year certified as being due to nasal sinus cancer, and it is unlikely that more than about half of these are due to all occupational causes of nasal sinus cancer put together, as an average of 158 such deaths also occurred each year in women. Moreover, no epidemic increases seem likely this century as even these small numbers are decreasing with the passage of time in both sexes. Nasal sinus cancers were not considered in the OSHA report. Had they been, the paradox of predicting that occupational exposure to nickel would cause more than ten times as many deaths to be attributed to nasal sinus cancer as could possibly be the case might have alerted the authors to the unsoundness of their methodology.

The argument that led to the projection of a further 7,300 excess lung cancers each year from current (1972–74) occupational exposure to inorganic arsenic (and therefore again to some 15,000 fatal lung cancers per year from ever-exposure to this agent) was along similar lines. To avoid any risk of misrepresentation, it too is reproduced verbatim from OSHA (1978):

> In 1969 Lee and Fraumeni evaluated the mortality experience of 8,047 white male smelter workers exposed to arsenic trioxide during 1938 to 1963. Smelter workers were found to have a three-fold excess in mortality from all respiratory cancer compared to a statewide population control group. About half of those in the study population were exposed to arsenic less than 10 years. Of those exposed for at least 15 years and followed another 25 years, the relative risk for respiratory cancer was 4.7. If this excess can be applied to the approximately 1,500,000 workers exposed to arsenic, it is projected that about 7,300 excess lung cancers each year may occur.

[1] The projected total of 33,000 incident cases of cancer per year ascribed to *current* (1972–74) exposure to nickel, arsenic, chromium, benzene, or other petrochemicals is assumed in the OSHA paper to correspond to 10–20% of 400,000–450,000 cancer deaths per year (i.e., about 64,000 deaths/yr) due to *ever*-exposure to those five agents. *See* section 5.6 for a more detailed description of this aspect of the arguments in the OSHA paper.

Similar risks have been reported for several other groups of copper smelters and for men engaged in the manufacture of pesticides in the United States and elsewhere, all of whom had been heavily exposed to inorganic arsenic in the course of their work. Only one study provides any basis for deriving a relationship between dose and effect and that on a most tenuous basis (Pinto et al., 1977). The World Health Organization (1980) recently used the results of this study to deduce that exposure to 25 μg of inorganic arsenic/m^3 of air at work for 25 years would double the normal risk of lung cancer, but this must be regarded as an overestimate of the effect because the measurements of pollution were made in 1973 at a time when, according to the authors, exposure had already been substantially reduced. Even without this qualification, however, it follows that the population of workers that was studied epidemiologically must have been regularly exposed to concentrations of the order of 100 μg/m^3, and it is impossible to believe that the 1.5 million workers who were said to be "currently exposed" to arsenic could be exposed to anything like that amount. These workers included electroplaters, farmers, jewelers, and plumbers in a list of 78 occupations with potential arsenic exposure published by the Department of Health, Education, and Welfare and include many who are exposed only to organic arsenicals, which have never been shown to cause cancer at all. The Occupational Safety and Health Administration (1976) had, in fact, already lowered its estimate of men and women potentially exposed to inorganic arsenic to about 900,000 of whom "a large number . . . work in areas where exposure to inorganic arsenicals are very low or nonexistent," and added that estimates of the number of directly exposed workers at any one time currently ranges from 1,500 to 1,700 for exposure levels of 100 μg/m^3 and above to 7,000 for exposure levels of 4 μg/m^3 and above. Using these dose estimates, one might finish up with an estimate rather similar to that of the American Industrial Health Council (1978), an organ of the chemical industry, which estimated that the maximum number of lung cancers induced by occupational exposure to arsenic that would occur over the next quarter of a century would be 15 a year: that is, about 0.2% of the figure of 7,300 ascribed to recent exposure (or 0.1% of the 15,000 or so ascribed to ever-exposure) in the statement filed at OSHA. In World War II it was possible to arrive at almost exactly the correct number of planes lost by enemy action on either side by calculating the geometric mean of the figures claimed by the British and German authorities. A similar technique would lead to an estimate of 331 lung cancer deaths from occupational exposure to arsenic each year. On the available evidence, however, this figure seems rather high.

For asbestos the authors used two assumptions: *a*) that 4 million American workers have had "heavy exposure to asbestos" since the beginning of World War II and that the proportion who have died or will die of lung cancer, pleural or peritoneal mesothelioma,

This article was commissioned as a report to the Office of Technology Assessment, U.S. Congress, to provide background material for their assessment of "Technologies for Determining Cancer Risks From the Environment" (OTA, 1981). It will be republished, by permission of the Editor in Chief of the JNCI, as an Oxford University Press paperback.

Acknowledgments

First and foremost, we wish to thank Mrs. Virginia Godwin for her assistance in preparing this report, and we are particularly indebted to Eugene Rogot, of the National Heart, Lung, and Blood Institute, for making available to us the data from the study of a quarter of a million U.S. veterans. Robert Fensterheim abstracted the cancer mortality data from 1933–78 from Government publications, and a tape of these data is available from R. Peto. The staff of the Populations Division of the Bureau of the Census provided corrected U.S. population estimates from 1950, Irene Stratton and Richard Gray analyzed the mortality data, and Cathy Harwood drew the figures. The Surveillance, Epidemiology, and End Results section of the Biometry Branch of the National Cancer Institute and the New York and Connecticut tumor registries kindly provided us with access to cancer incidence data. Finally, we wish to thank the dozens of known or anonymous scientists who, through us or through the Office of Technology Assessment, scrutinized and offered helpful criticism of previous versions of this report.

ABBREVIATIONS USED: ACS = American Cancer Society; AF2 = 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide; CPEAP = Committee on Prototype Explicit Analyses for Pesticides; DAB = *p*-dimethylaminoazobenzene; DES = diethylstilbestrol; DMBA = 7,12-dimethylbenz[*a*]anthracene; EPA = Environmental Protection Agency; GESAMP = Group of Experts on the Scientific Aspects of Marine Pollution; IARC = International Agency for Research on Cancer; ICD = International Classification of Diseases; NAS = National Academy of Sciences; NCI = National Cancer Institute; NIOSH = National Institute of Occupational Safety and Health; NIEHS = National Institute of Environmental Health Sciences; OSHA = Occupational Safety and Health Administration; PVC = polyvinyl chloride; SEER = Surveillance, Epidemiology, and End Results program of NCI; SNCS = Second National Cancer Survey; TNCS = Third National Cancer Survey; TSSC = Toxic Substances Strategy Committee; WHO = World Health Organization.

1981). If these results are applicable nationally (and the similarity of the incidence rates suggests that they are), it follows that some 500–600 mesotheliomas were caused by asbestos each year between 1970 and 1975.

Even though mesotheliomas are probably underdiagnosed, and even though the incidence of mesotheliomas among men is increasing, it seems most unlikely that as many as 1,000 per year could be currently caused by asbestos.[4] In other words, there is at least a tenfold exaggeration in the OSHA estimates of the numbers of mesotheliomas due to asbestos and, consequently, in their estimates of the other cancer hazards of asbestos.[5] Errors by at least a factor of 10 were also present in the OSHA estimates of the effects of arsenic and nickel, and no reasons are given for supposing that the errors in their treatment of chromium, benzene, or other petrochemicals were any less extreme.

These straightforward arguments are not accepted by people who wish to emphasize the importance of occupational factors (e.g., the Toxic Substances Strategy Committee in its 1980 report to the U.S. President, or Epstein, 1981a, 1981b), although it would be more accurate to say that these arguments are not addressed by such people. The arguments have, however, been discussed with many epidemiologists and have been accepted by most. They are reinforced, as far as asbestos is concerned, by the experience of chest physicians whose clinical practice demonstrates the falsity of the proposition that half their patients with respiratory cancer have had occupational exposure to significant amounts of asbestos which, in three-quarters, could be described as heavy.

REFERENCES

See pages 1260–1265.

[4] That some mesotheliomas are miscertified as other types of cancer [68% in Selikoff and Seidman's (1980) detailed study] is evident. It is notable, however, that in the recent study of mesotheliomas in residents of a coastal town in Virginia where there were several large shipyards (Tagnon et al., 1980), the incidence of mesothelioma determined from discharge diagnoses, pathology files, tumor registries, and the records of local physicians was not elevated above the nationally recorded rate (Hinds, 1978) for black males and black and white females and was increased only four times for white males among whom (to judge by the control group) 28% at the ages studied had been employed in shipbuilding. It is, therefore, probably generous to double the national figure.

[5] At the 1981 Cold Spring Harbor Laboratory meeting on the Quantification of Occupational Cancer, the speakers in the session devoted to asbestos came from a range of backgrounds (including Dr. Selikoff's department at New York, the National Cancer Institute, and various industries and universities). Using some quite different epidemiological approaches, several of these speakers devised numerical estimates of the proportion of U.S. cancer deaths currently due to asbestos, all of which were around 1 or 2% (rather than 15–18%!), and no speaker or participant dissented from this consensus.